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14. ABSTRACT

Although selective serotonin reuptake inhibitors (SSRIs) are routinely prescribed for acute stress disorder and early PTSD and recommended in the VA-DoD best practice guidelines, the efficacy of SSRIs as an early intervention for PTSD in service members returning from war-zone duty has still not been determined. Consequently, this study was designed to conduct a controlled trial of fluoxetine as an early intervention for recently redeployed soldiers, as well as to develop methodologies for understanding the multiple factors that may predict outcome. The study was conducted at two sites: Carl R. Darnall Army Medical Center and Central Texas Veterans Health Care System. Despite recruitment efforts, only 42 participants were enrolled. Of these, 18 were randomized. The limited enrollment obscures interpretation of the results. No unexpected side effects were observed. Our data does not support or refute the use of SSRIs for treatment of PTSD.

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Fluoxetine, Posttraumatic Stress Disorder, Antidepressants

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INTRODUCTION:
Although selective serotonin reuptake inhibitors (SSRIs) are routinely prescribed for acute stress disorder and early PTSD and recommended in the VA-DoD best practice guidelines, the efficacy of SSRIs as an early intervention for PTSD in service members returning from war-zone duty has still not been determined. Consequently, this study was designed to conduct a controlled trial of fluoxetine as an early intervention for recently redeployed soldiers, as well as to develop methodologies for understanding the multiple risk factors that may predict outcome. Fluoxetine was selected as the psychopharmacologic agent for this study because it is well tolerated, it has a very favorable cost-benefit advantage as a generic drug, and the fact that it is the only SSRI with at least preliminary studies demonstrating its efficacy in recent-onset, war-related PTSD. Studies focusing on targeting chronic combat-related PTSD with SSRIs have shown mixed results with some small open-label studies suggesting efficacy, while two controlled trials with Vietnam veterans were negative. Because in all prior trials there is considerable variability of response to fluoxetine, we planned to examine several predictors of efficacy. We argued that the efficacy of SSRIs for recently redeployed soldiers at risk for chronic PTSD is moderated by multiple personal, deployment, and environmental factors. It was expected that not all subjects would respond to fluoxetine. For those that did not respond to fluoxetine alone, augmentation with either buspirone or bupropion was offered based on their reasonable tolerability, low cost and the recent findings documenting their utility as adjunctive treatments for depression.

BODY:
Approval was obtained from the Brooke Army Medical Center IRB, the regional IRB for the Carl R. Darnall Army Medical Center (CRDAMC), as well as the Central Texas Veterans Health Care System (CTVHCS) IRB and their Research and Development Committee. A Cooperative Research and Development Agreement (CRADA) between TEMPVA Research Group, Inc. and CRDAMC was executed. The protocol was also approved by the Human Research Protection Office (HRPO) of the Office of Research Protections (ORP) U.S. Army Medical Research and Materiel Command (USAMRMC) Fort Detrick. PR064845 was registered in ClinicalTrials.gov, No. NCT00633685. VA donated the use of an administrative trailer (12'X52') to provide sufficient office space to perform the study. Recruitment was pursued through the CRDAMC Restoration and Resilience Center and the CTVHCS PTSD Clinical Treatment Clinic by referrals, flyers, mailings, and public broadcast messages (Ft. Hood radio and television systems). Information regarding the study has been presented to 179 potential participants by direct contact. Of those, 43 signed a consent form. Of the 43 that signed a consent form, 25 met exclusion criteria and 18 were randomized. Of the 18 randomized, 4 completed all 32 weeks of the trial (Phase I and Phase II). In the fluoxetine-treated group only 2 completed the Phase I trial, and in the placebo group only 6 completed the Phase I trial. The very limited enrollment and high drop-out rate makes data analysis and interpretation of the findings impossible. Figures 1-3 display the observations for the primary and secondary outcome measures with the last observation carried forward. Because several patients in the fluoxetine group dropped out of the study before completion of scheduled observations, most of the Clinician Administered PTSD Scale (CAPS) scores and PTSD Checklist (PCL-M) means for the fluoxetine group reflect only scores carried forward from early in treatment trial. Any perceived difference from the placebo group is not justified. With this small sample, the fact that more individuals dropped out of the fluoxetine group is coincidental. Drop outs were mostly for non-treatment-related reasons (lost to follow-up, deployment, etc.). The pre-determined definition of a responder (50% decrease in the PCL-M) was met by only 2 of the 18 randomized participants. Both were in the placebo group. On the Beck Depression Inventory-II (BDI-II), 6 placebo-treated and 1 fluoxetine-treated participant had a greater than 50% drop in the baseline score. More in keeping with expectations, 3 placebo-treated participants had a worsening of their baseline BDI-II, but only 1 fluoxetine-treated participant. Baseline assessments of Repeatable Battery for Assessment of

Neuropsychological Status (RBANS), AUDIT-C, CAPS, and PCL-M did not differ between treatment groups. There was a marginal difference in the baseline scores on the Connor-Davidson Resilience Scale (CD-RISC) with the fluoxetine group average score of 62±4.6 (X±SEM) and the placebo group averaging 50±2.9 ($p<.05$, $t=2.2$). This difference does not appear to be clinically significant, and was present only at baseline.

The difficulty in recruitment appears to be related to a variety of factors. There was considerable reluctance of clinical staff to refer to a trial that involved the potential for a placebo assignment, despite the design that included careful and frequent monitoring of participants. Most of the patients with the diagnosis of PTSD in both CRDAMC and CTVHCS were already on complex pharmacotherapies prior to recruitment attempts, perhaps because of the fact that by the time the study began recruitment most potential recruits were exposed to antidepressants in the war theater. Providers were remarkably unwilling to consider re-starting pharmacotherapeutic interventions. Many of the individuals who did express interest in enrollment were already past the time interval targeted for inclusion (3 years from onset of symptoms). The time commitment for service members was difficult to manage resulting in many dropping out of the study or refusing enrollment. It appears that insistence on a double-blind, placebo-controlled trial was the weakness of our effort. The need for understanding the effectiveness of SSRIs in the management of PTSD still remains. In retrospect, despite the scientific advantages to a controlled trial, the aim of learning how to predict response to fluoxetine could possibly have been more successfully addressed by an open-label trial with an independent evaluator unfamiliar with the study design.

In addition to the Project Tasks, a review of the pharmacotherapy literature for PTSD was prepared, although it has not yet been published Appendix B.

Project Tasks:

Task 1: Submission of the Proposal to the IRBs

- The proposal must be approved by both the Brooke Army Medical Center IRB and the Central Texas Veterans Health Care System Human Subjects Subcommittee.
- **Completed**

Task 2: Recruitment and Training of Study Personnel

- Hire two master's prepared research assistants
- Training on recruitment procedures and research assessments (SCID, CAPS, etc.)
- **Completed**

Task 3: Preparation of Over-Encapsulated Blinded Medications for the First Phase of the Clinical Trial

- Purchase of the fluoxetine and gelatin capsules from VA pharmacy suppliers (purchased each 3 months throughout the first 15 months of the study)
- Over-encapsulation of fluoxetine and empty gelatin capsules by CTVHCS Pharmacy staff
- Transfer of medications prepared by the CTVHCS Pharmacy directly to the Carl R. Darnall Medical Center Pharmacy
- The Fluoxetine and placebo capsules have been prepared and transferred to the CRDAMC Pharmacy.
- **Completed**

Task 4: Recruitment/Clinical Trial

- Enrollment of a minimum 20 subjects per month for 15 months
- Double-blind, placebo-controlled trial of fluoxetine + usual psychological care for 12 weeks
- Open-label extension of the fluoxetine trial for 20 weeks
- **Enrollment has been stopped because we have not been successful in recruitment goals**

Task 4: Data Collection and Transfer to the Boston VA National PTSD Research Center

- Data will be stored on compact discs for storage
- Compact discs will be sent on a monthly basis to the National PTSD Research Center for database development
- The post-doctoral fellow working with Dr. Brett Litz will maintain the database under the oversight of Dr. Litz
- **Dr. Litz's group helped set up our database**

Task 5: Data Analysis at the Boston VA National PTSD Research Center

- **Only summary statistics were possible with the limited data collected**

List of personnel receiving salary from this study:

- Leah Blackburn, M.A., L.P.C.
- John Reeve, Ph.D., L.P.C.
- Natalie Reeves, M.A., L.P.C.
- Kamau Richard, M.A., L.P.C.
- Beate Medina, M.A.

KEY RESEARCH ACCOMPLISHMENTS:

- No significant differences were identified between treatment groups on any of the outcomes measures because of insufficient power resulting from the low enrollment

REPORTABLE OUTCOMES:

- P. B. Hicks. Pharmacotherapy of Posttraumatic Stress Disorder and Traumatic Brain Injury. In ***Neuropsychology of PTSD and mTBI***, eds. S. Dolan, S. B. Gulliver, and S. Martindale, Oxford University Press. *In press* (see Appendix A).

CONCLUSIONS:

- With limited recruitment conclusions about pharmacotherapy with SSRIs is unwarranted.
- Despite the scientific advantages to a controlled trial, the Aim of learning how to predict response to fluoxetine should be addressed by an open-label trial with an independent evaluator unfamiliar with the study design.

REFERENCES: Not applicable.

APPENDICES:

- Appendix A: P. B. Hicks. Pharmacotherapy of Posttraumatic Stress Disorder and Traumatic Brain Injury. In ***Neuropsychology of PTSD and mTBI***, eds. S. Dolan, S. B. Gulliver, and S. Martindale, Oxford University Press. *In press.*

Pharmacotherapy of Posttraumatic Stress Disorder and Traumatic Brain Injury

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Pharmacological management of Posttraumatic Stress Disorder (PTSD) has been the focus of several recent reviews. [1,2,3,4,5,6,7,8,9] In addition, guidelines have been widely distributed: (1) International Psychopharmacology Algorithm Project (http://www.ipap.org/algorithms.php; 2005); and (2) Department of Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guidelines for the Management of Post-Traumatic Stress Disorder (http://www.healthquality.va.gov/Post_Traumatic_Stress_Disorder_PTSD.asp; 2010). Similarly, there have been multiple reviews of the pharmacotherapy of TBI. [10,11,12] This chapter will describe our current understanding of pharmacotherapy of these conditions, as well as highlight the limits of our knowledge so that a rational approach to the pharmacotherapy of these conditions can be achieved.

A. Treatment of PTSD

The current guidelines for the pharmacotherapy of PTSD focus on the use of antidepressants as first line treatment. Various alternative/adjunctive medications are also recommended for those situations in which symptoms are not completely controlled. While these approaches appear to be straightforward, there are several factors that should be considered in the implementation of these guidelines. First, PTSD is generally agreed to exhibit three symptom clusters: re-experiencing of the trauma (intrusive memories, images or perceptions; nightmares; flashbacks; exaggerated emotion and physical reactions), avoidance/emotional numbing (avoidance of activity, loss of interest, detachment, and restricted emotion), and increased physiological arousal (difficulty sleeping, irritability, difficulty concentrating, hypervigilance, and exaggerated startle response). Whether symptoms clusters could differentially respond to specific pharmacological interventions has not been fully determined. Second, there is a progressive staging of the onset of chronic PTSD: (1) Acute Stress Reaction (less than 3 days

duration), (2) Acute Stress Disorder (more than 3 days and less than one month), (3) Acute PTSD (at least one month and up to three months), and (4) Chronic PTSD (greater than three months; in this chapter referred to as "PTSD"). It is possible that the pharmacological interventions required to mitigate the progression from one stage to the next may differ at the various stages. Third, the clinical wisdom of the need to choose the correct drug for an individual patient, prescribed at a sufficient dosage, and administered for greater than the minimally required duration should hold for the treatment of chronic PTSD. No method has been developed to determine how to choose the correct drug for each individual, or to guide the choice of minimum drug dosage. Fourth, PTSD can be caused by a wide variety and complexity of traumatic events. Some develop PTSD based upon single traumatic exposures. However, especially in the cases of childhood sexual abuse or combat-related PTSD, PTSD is developed based upon traumas that may be chronic and associated with extended periods of high probability of future threat. Demographically, sexual abuse almost exclusively happens to children who then live and cope with the aftermath of the traumas not only in childhood but also in adulthood. Combat-related PTSD, in contrast, is mostly a problem of adults who may or may not have experienced abuse as a child. In fact, few studies have exclusively focused on a select population when addressing pharmacological management of PTSD, except for the several studies on combat-related PTSD. Whether the pharmacological management should be different based upon the duration or type of the trauma exposure needs to be determined. Fifth, when the primary intervention is not completely effective we need to understand what augmenting agents should be used for control of PTSD symptoms. Finally, there is minimal guidance available on the treatment required to sustain remission of symptoms, or determine when pharmacological

intervention may be discontinued. In this chapter we will review the available evidence to address each of this issues.

1. Should Pharmacotherapy Differ for Management of the Various PTSD Symptoms?

Diminishing the re-experiencing of the trauma and hyperarousal are major concerns in the pharmacotherapy of PTSD. Understanding the pathophysiology of the re-experiencing of trauma and hyperarousal helps to shed light on how to approach attempts to modulate this symptom complex. Noradrenergic hyperactivity is likely the substrate for the re-experiencing of traumas, as well as the hyperarousal state. [13,14,15] While demonstration of increased noradrenergic activity in the brains of individuals with PTSD is difficult to measure directly, there is considerable indirect evidence that suggests noradrenergic hyperactivity is present. Cerebrospinal levels norepinephrine (NE) and twenty-four hour urinary catecholamine levels in individuals with PTSD are usually determined to be greater than normal controls. [16,17] Consistent with these findings, individuals with PTSD treated with yohimbine, an alpha-2 antagonist that is known to increase release of NE from noradrenergic terminals, have an exaggerated response with up to 40% experiencing flashbacks during a yohimbine challenge. [18] Also, neuropeptide Y (NPY), a 36-amino acid peptide neurotransmitter which functions to inhibit NE release, is known to co-localize with NE in the locus coeruleus, amygdala, hippocampus, periaqueductal grey, and prefrontal cortex. [19] Individuals with PTSD have lower baseline plasma NPY levels and exhibit a diminished yohimbine-stimulated increase in plasma NPY levels in comparison to controls. [20] Conversely, special-forces soldiers, presumably more resistant to the development of PTSD, who receive military survival training were more likely than non-special forces soldiers to elevate plasma NPY levels. [21] These findings are consistent with the hypothesis that diminishing the re-experiencing of traumas may require decreasing NE activity. Also consistent with this

hypothesis is the efficacy of selective serotonin reuptake inhibitors (SSRIs). Serotonergic projections for the dorsal raphe nucleus inhibit the firing of the locus coeruleus, [22] the brain nucleus that contains the cell bodies of the noradrenergic projections to the forebrain; and, therefore, the increase in serotonergic activity that accompanies SSRIs would be expected to diminish the NE hyperactivity seen in PTSD.

There are a variety of mechanisms possible for diminishing brain NE activity including: (1) blocking NE receptors, (2) diminishing the release of NE from pre-synaptic terminals, (3) activating neural pathways that inhibit locus coeruleus activity, and (4) inhibiting the synthesis of NE. The first three mechanisms are the strategies that have received by far the most attention. Prazosin, an alpha-1 adrenergic antagonist, in high doses has been shown to have efficacy for the treatment of a variety of features of PTSD, especially nightmares. [23,24,25] The initial report on 10 Vietnam era combat veterans with chronic PTSD in a 20-week, double-blind crossover protocol indicated that high doses (up to 10 mg daily) resulted in significant improvements in Clinician Administered PTSD Scale (CAPS) item scores (decreasing recurrent distressing dreams by 48%, difficulty falling/staying asleep by 46%, avoidance/numbing by19%, hyperarousal by 31%, and a total CAPS score by 28%). [25] Most participants were also rated as demonstrating that they were moderately improved on the Clinical Global Impression (CGI) scale. A second double-blind, placebo-controlled study from the same group confirmed a clinically significant (51%) decrease in the CAPS recurrent distressing dreams item score. [24] Similar results were found in a double-blind crossover trial of civilian patients with chronic PTSD using lower prazosin doses (average daily dose of 3 mg). [26] Interestingly, adverse events from these studies were generally mild, limited to infrequent, non-symptomatic orthostasis.

The efficacy of an alpha-1 adrenergic antagonist suggests that other compounds that act to diminish noradrenergic activity may have promise as therapeutic agents in PTSD. Alpha-2 agonists such as clonidine and guanfacine act by inhibiting the release of NE at synapses by action at noradrenergic autoreceptors. In fact, clonidine was shown to have efficacy in controlling hyperarousal, hypervigilance, sleep disruption, exaggerated startle responses, and nightmares in open label trials in combat veterans with PTSD, [14] and increased the effectiveness of imipramine in an open trial in Cambodian refugees with PTSD. [27] Other open label studies suggest that clonidine may decrease nightmares in pediatric patients with abuse-related PTSD; [28,29] and likewise another centrally active alpha-2 agonist, guanfacine, may reduce nightmares in children with PTSD. [30,31] Unfortunately, despite these early encouraging results, controlled trials evaluating the efficacy of clonidine have not been reported, and two controlled trials with guanfacine demonstrated a lack of efficacy. [32,33]

Other compounds that have clinical utility for the management of re-experiencing trauma (e.g. nightmares) or hyperarousal (e.g. sleep disturbance) associated with PTSD, trazodone and quetiapine, also exhibit significant alpha-1 adrenergic blockade. Trazodone and quetiapine actually have about one-tenth the alpha-1 adrenergic blockade activity as prazosin, [34] but are generally prescribed in doses that are an order of magnitude greater than prazosin – suggesting they would offer equivalent alpha-1 adrenergic blockade. Positron emission tomography (PET) studies, which would be definitive in comparing relative central alpha-1 adrenergic receptor occupancy of these compounds in vivo, have not been performed. Based on the binding studies and absent PET data to the contrary, one can only assume, then, that all three of these compounds have significant alpha-1 adrenergic blockade in clinically relevant doses. If the benefits of prazosin were based solely on the alpha-1 adrenergic mechanism, then one would

expect equivalent benefits from trazodone and quetiapine. In fact, trazodone has been recognized as an agent that improves sleep and overall CAPS scores in patients with chronic PTSD, [35] and trazodone is commonly prescribed for sleep in patients with PTSD. [36] While some efficacy is likely, there are no trials comparing the benefits of trazodone with prazosin or other alpha-1 adrenergic blocking agents. It should be noted that some caution is required in prescribing trazodone because of the uncommon (1 in 5000) risk of priapism, but it certainly is another inexpensive alternative for management of sleep disturbance/nightmares in PTSD. Although trazodone and prazosin have not been compared in clinical trials, there is a recently published retrospective study comparing prazosin and quetiapine. [37] Both showed efficacy in controlling nightmares and improving sleep, however prazosin was generally better tolerated and resulted in significantly fewer discontinuations (18% vs. 35%; p=.008). Because of the retrospective nature of this comparison, final judgment about differences in efficacy or tolerability should await prospective trials.

Based on the efficacy of alpha-1 adrenergic antagonists for controlling nightmares, they have been increasingly recommended when nightmares or sleep disturbance do not respond to antidepressants. This is critical because one of the most important targets for the pharmacologic management of PTSD is sleep disturbance, often associated with trauma-related nightmares. In fact, over 90% of Vietnam combat veterans report sleep disturbance with over half reporting nightmares; [38,39] while approximately 80% of all individuals with PTSD report nightmares during the course of their illness. [40]

In addition to alpha-1 adrenergic antagonists, several other pharmacologic approaches have been recommended. [41] Benzodiazepines or similar sedative-hypnotics are no longer promoted for use in treatment of PTSD, but are often used in the initial stages of treatment. [42] While trials

with benzodiazepines have been uniformly disappointing for overall effects on the core symptoms of PTSD, [43] some modest benefit has been noted in decreasing the difficulty initiating and maintaining sleep. [44] Another early approach to the management of PTSD-associated nightmares that is no longer recommended is the use of cyproheptadine. Preliminary open label reports of the use of cyproheptadine (4-12 mg at bedtime) were promising for treatment of nightmares associated with PTSD. [45] However, a larger open label trial from another group, using 4-8 mg at bedtime did not find cyproheptadine to be effective; [46] and a moderate-sized randomized, controlled trial of the use of cyproheptadine in Vietnam era veterans demonstrated that sleep disturbance and nightmares might actually increase with cyproheptadine. [47]

PTSD Criterion C symptoms (avoidance of activity, loss of interest, detachment, and restricted emotion) could be another focus of pharmacotherapy, and are known to be responsive to treatment with SSRIs. [7,48] In fact, the Stein, et al. [7] review demonstrates that all antidepressants with effectiveness in alleviating symptoms of chronic PTSD appear to have modest but measureable benefits in controlling these symptoms, as well as effects of the same order of magnitude on re-experiencing or hyperarousal symptoms. Equivalent results are evident whether the CAPS or self-reported measures are used to assess these symptoms. No classes of medications have been found to be selectively helpful for management of avoidant behaviors in the treatment of PTSD, however.

It appears that medications that as yet have been proven to be effective for the management of PTSD do not have selective efficacy on the various features of PTSD. Instead, SSRIs and most other antidepressants do have broad-spectrum benefits for the various PTSD symptom complexes. Drugs that block central alpha-1 adrenergic receptors, e.g. prazosin, quetiapine and trazodone, have benefit for management of nightmares and sleep disturbance in PTSD, and are

often used for management of these specific features of PTSD. However, these compounds also have more general effects on the symptomatology of PTSD. Perhaps we will be able to identify medications that have more selective benefits for specific features of PTSD as we better understand its pathophysiology.

2. What Differences in Pharmacotherapy Approaches Should Be Used at each Stage of the Development of Chronic PTSD?

a. Acute Stress Reaction

The pharmacotherapy of the prevention of the development of PTSD after trauma exposure (secondary prevention) is not well developed, but includes attempting to diminish memory consolidation and conditioned fear responses following a traumatic event, facilitating extinction of traumatic memories, or dissociating the emotional response from the traumatic memory. [49] The N-methyl-D-aspartate (NMDA) glutamate receptors play a key role in the consolidation of memory, but also promote extinction of memories that have already been established. [50] One approach to the prevention of PTSD is to interrupt the consolidation of traumatic memories, and thus prevent their establishment. NMDA antagonists would be expected to interfere with memory consolidation. [51] Ketamine is a reversible NMDA antagonist that is sometimes used as an anesthetic agent. In an observational study of 147 OEF/OIF injured soldiers (119 received ketamine and 28 did not), reported rates of PTSD development were lower for those receiving ketamine (27%) versus no ketamine (46%). [52] Prospective trials are lacking, however.

Ketamine should interfere with memory consolidation, while NMDA agonists should promote memory extinction. The NMDA receptor requires glycine for full activity. D-Cycloserine (DCS) is known to act as a selective, albeit partial, glycine agonist; [52,53] and, in at least one preliminary trial, DCS facilitated extinction of fear responses in another anxiety

disorder (acrophobia). [54] Based upon the possibility that DCS might similarly promote extinction of established PTSD, a 12-week, double-blind, placebo-controlled crossover pilot study in 11 individuals with PTSD resulting from a variety of traumatic events (mostly traffic or work-related accidents) showed DCS (50 mg daily) was ineffective in reversing the symptoms of PTSD. [53] Unfortunately, any potential benefits identified for use of DCS were also present to the same degree with placebo exposure. The same group performed a second pilot study (6-week double-blind, placebo-controlled, crossover trial) in 22 chronic PTSD outpatients given DCS at 30 mg/kg daily as monotherapy or add-on pharmacotherapy. [55] DCS treatment resulted in significantly reduced Mississippi Scale for Combat-Related PTSD ($p=.001$) scores and a trend towards improved CAPS total scores ($p=.07$), suggesting that this strategy warrants further consideration. These studies have not addressed whether the timing of the intervention may influence responsiveness to DCS, but further trials of DCS are expected.

Use of morphine to interfere with fear conditioning in the development of PTSD is another potential approach to secondary prevention of PTSD. [56,57] Morphine is known to impair acquisition of fear conditioning when injected directly into the amygdala, [58] and attenuates NE turnover in the amygdala and basal ganglia of stressed rats. [59] These findings suggest that morphine could be useful to prevent the development of PTSD. Preliminary findings are consistent with this hypothesis. In a study of 696 Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) soldiers, where a diagnosis of PTSD was made from recorded chart diagnoses 1-24 months after the injury, morphine administered intravenously in low to moderate doses (median dose of 5 mg) immediately following the trauma, decreased the likelihood of subsequently developing PTSD by approximately half (odds ratio of 0.47). [56] The finding was still present when adjusting for injury severity, age, mechanism of injury, status with respect to

amputation, or the presence of traumatic brain injury. Similarly, a study in acutely injured children demonstrated that morphine had a protective effect on the development of PTSD. [57] In a third study, consecutive patients admitted to a hospital after traumatic injury (N=155) were assessed for current psychiatric disorder, pain, and morphine dose in the initial week after injury and reassessed for PTSD and other psychiatric disorders 3 months later (N=120). [60] Of the 17 patients that met criteria for PTSD at 3 months, significantly less morphine had been given to them in the acute post-injury period. This study also corroborated the work of Norman, et al. [61] that those individuals experiencing greater pain intensity are at greater risk of development of PTSD. A logical expectation would be that those with the greater pain intensity would be the most likely to receive morphine and other opiates. It also possible those with greater pain intensity were exactly those receiving inadequate morphine; and, therefore, should be expected to have greater incidence of PTSD. Clearly, further studies are important to clarify these relationships. However, using morphine immediately following an injury should be encouraged when the injury is associated with significant pain and likely to result in development of PTSD.

Recall of traumatic memories can be influenced at various levels including: (1) formation/acquisition/encoding of the memory; (2) encoding of the emotional response and consolidation of the memory; and (3) reconsolidation/reinstatement/retrieval of the memory, which includes recall of the emotional responses triggered by trauma-associated stimuli. [49] Propranolol, a beta-adrenergic antagonist, appears to interfere with the encoding of the emotional response associated with encoding and retrieval of emotional memory, and therefore has been proposed as a potential pharmacological intervention in the secondary prevention of PTSD. [62] For example, when participants were asked to view a set of slides accompanied by either an emotional or neutral story, propranolol affected the retrieval of information only for the

emotional story. [63,64] Using the same paradigm, it was found that activation of the amygdala by emotional stories was attenuated by propranolol. [65]

The timing of administration appears to be critical. In the studies where propranolol appears to have a significant effect, it was administered within six hours of the traumatic event. When administered later, the results are generally negative. For example, when propranolol (20 mg daily) or hypnotic agents were given to survivors of the March 11, 2004 terrorist attack in Spain who had already developed Acute Stress Disorder, [66] there was no difference in the remission rates between the two groups. Similarly, the administration of propranolol up to 4 mg/kg/day during the first 10 days and sustained for the first four weeks in pediatric burn patients did not affect the incidence of Acute Stress Disorder. [67] Administration of propranolol also did not diminish the incidence of PTSD in soldiers that were burn victims. [68] However, a pilot study of individuals treated within 6 hours of a traumatic event with 40 mg propranolol and continued on the same dose 4 times daily for 10 days demonstrated that those treated with propranolol exhibited less reactivity to a script in the patient's own words of the traumatic event. [69] In a similar small study, those that refused use of propranolol but remained in the study for observation, were much more likely to later develop PTSD (38%) than those that agreed to take propranolol (9%). [70]

These acute intervention studies suggest that pharmacological approaches to secondary prevention do have merit, and should be pursued in larger clinical trials – especially studies of ketamine, morphine, and propranolol.

b. Acute Stress Disorder

There are few studies directly addressing pharmacological management of Acute Stress Disorder. However, in two open label trials, the antipsychotic risperidone was used for treatment

of Acute Stress Disorder in children or adults with burn injuries sufficient to require hospitalization. [71,72] Risperidone was shown to have immediate benefit in controlling sleep disturbance, frequency of nightmares and flashbacks, and hyperarousal. In these initial trials, the long-term outcome was not monitored making it impossible to know if decreasing the symptomatology of ASD would prevent progression to PTSD. Also, studies did not specifically address whether the alpha-1 adrenergic blocking action or dopamine blocking action is of importance in the outcome.

c. Acute and Chronic PTSD

There are no studies that focus specifically on pharmacotherapy approaches for Acute PTSD that are not already used in Chronic PTSD, and therefore further discussion will focus on the pharmacotherapy of Chronic PTSD. Psychotropic medications are very commonly prescribed for management of PTSD. [42,73] Approximately 80% of patients treated in Veterans Administration (VA) hospitals for PTSD receive a psychotropic. In a private sector population, that figure may only be 60%. It should not be overlooked that VA populations with PTSD are mostly those with combat-related PTSD. Despite the recent wars, there are still more Vietnam era veterans than Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans, and most studies evaluating the use of psychotropics for PTSD in combat veterans were performed prior to a time when the recent combat veterans could be available for study. Therefore, VA population statistics are heavily influenced by individuals with very chronic symptoms. Of those receiving psychotropic medications, over 80% in VA populations and over 70% in private populations receive antidepressants. If an antidepressant is prescribed, it is most likely an SSRI. Sedative hypnotic use is slightly more common in private populations (74%) than VA populations (61%). Antipsychotic agents are also used to a lesser extent in private

populations (34% VA patients and 21% private populations). Although antipsychotic use appears to be high, these data do not inform us on when the antipsychotics are used solely for their sedating properties.

The majority of studies indicate that most antidepressants have efficacy for treatment of PTSD [1,2,3,4,5,6,7,8,9,74] with the possible exceptions of bupropion [75] and some reversible monoamine oxidase inhibitors. [76] As will be seen later, the presumed lack of efficacy of these compounds may only be a function of inadequate data to definitively assess efficacy of these medications.

(1) Selective Serotonin Reuptake Inhibitors (SSRIs)

Based on their favorable side effect profile and safety in overdosage, SSRIs remain the recommended first line treatment for PTSD. While only paroxetine and sertraline have an FDA-approved indication for management of PTSD, [77,78,79] all other SSRIs have been demonstrated to have efficacy, including citalopram, [80] fluoxetine, [81,82] and fluvoxamine. [83,84,85]

Sertaline has been the best studied SSRI with at least five double-blind, placebo-controlled trials of the use of sertraline for treatment of PTSD, [77,79,86,87,88] as well as open-label studies. [89,90] Typical results demonstrate a 10-point or greater decrease in the total Clinician Administered PTSD Scale (CAPS)-2 score over placebo in a 12-week treatment period. One of the most definitive studies was a 12-week, double-blind, placebo-controlled trial preceded by a 2-week, single-blind placebo lead-in period. [77] A total of 187 outpatients with a diagnosis of PTSD and a Clinician Administered PTSD Scale Part 2 (CAPS-2) minimum total severity score of at least 50 at baseline were randomized to acute treatment with sertraline (flexible daily dosages of 50 to 200 mg daily, sertraline N=94; or placebo N=93). Sertraline treatment resulted in greater improvement than placebo on the primary outcome measure (CAPS-2 total score, p=.02). Similar results are found in the other studies. The results of these studies make it clear that there

is benefit to using this SSRI.

The largest study of treatment of PTSD with an SSRI was a 12-week trial with paroxetine. [78] In this study, outpatients with chronic PTSD were randomly assigned to take placebo (N=186), or paroxetine (N=183 for 20 mg/day and N=182 for 40 mg/day). Efficacy was assessed by examining the change in total score from baseline to endpoint on the CAPS-2. All groups had improvement in total CAPS-2 scores, but the paroxetine treated groups improved about one-half standard deviation greater than the placebo group. The 40-mg dose group fared no better than the 20-mg dose group. In this study, there were approximately two-thirds of those enrolled were women, and approximately one-half were victims of physical or sexual assault. The magnitude of benefit did not differ by PTSD symptom complex. A second, 12-week, flexible-dose study, compared paroxetine use at 20-50 mg daily (N= 151) to placebo (N= 156). [91] Paroxetine was superior to placebo as measured by the CAPS total score. In addition, the proportion of individuals meeting a priori criteria for response was greater for paroxetine (59%) than placebo (38%). In both studies the percent completing the trial was over 60%, consistent with paroxetine being generally well tolerated.

The efficacy of fluoxetine for treatment of PTSD is less well established, primarily because there have been fewer large clinical trials. The largest fluoxetine trial was performed in Europe (N = 301). [81] In this 12-week, flexible dose, double-blind, placebo-controlled trial, fluoxetine was given in doses up to 80 mg daily (X=57 mg daily). The primary outcome measure was the Treatment Outcome PTSD-8 (TOP-8) Score. Fluoxetine (N=226) was superior to placebo (N=75) as measured by the TOP-8 and total CAPS-2 scores. Interestingly, the participants included nearly half (48%) combat-related PTSD. The same group performed a second study that specifically targeted combat-related PTSD and also found improvements with the use of

fluoxetine. [82] A 24-week relapse prevention phase followed the initial 12-week trial. [92] Of those patients switched to placebo, 26% became symptomatic of their PTSD again while only 3% of those remaining on fluoxetine became symptomatic. Interestingly, the last published report from this group was a fixed dose, double-blind, placebo-controlled study with negative findings. [93] The individuals in the negative study were recruited from 43 sites in the U.S. The maximum dosage of fluoxetine allowed was 40 mg daily, which is nearly 20 mg less daily than the average daily dose in the two previous positive studies – suggesting higher doses of fluoxetine appear to be required for the best fluoxetine response in patients with PTSD.

An early study of the use of fluoxetine for treatment of PTSD raised the possibility that there was greater risk of increased anxiety and exacerbation of panic attacks than might be expected with other SSRIs. [94] This study included many patients with high co-morbidity of panic disorder (58%) and depression (84%). However, subsequent studies have demonstrated that fluoxetine is tolerated well in patients with PTSD. [81,92,95] In a study specifically designed to test the tolerability of fluoxetine, subjects with PTSD were given fluoxetine in a double-blind, placebo-controlled trial evaluating treatment-emergent symptoms. [95] The only treatment-emergent symptom that occurred with significant frequency was nausea (30%). No patients dropped out of the study because of nausea, and only one patient (3%) dropped out of the study because of a sense of activation. A drop-out rate of less than 5% because of treatment-emergent side effects was also found in the other studies of fluoxetine for PTSD. [81,92] Dropout rates for studies with sertraline or paroxetine have generally been of the same magnitude (<10%) and also associated with diarrhea or nausea. [96,97] However, the lack of head-to-head comparison trials between SSRIs make it difficult to assess relative efficacy or safety differences among the SSRIs.

Venlafaxine is an antidepressant that has significant SSRI activity, although it also has some

norepinephrine reuptake inhibition activity. A large, multi-center, multi-national, 24-week, flexible dose, placebo-controlled trial of the use of venlafaxine was conducted entirely outside the U.S. [98] Participants were slightly more likely to be women (53%), and had a mean age of 41 years. Significant improvement was seen for both the venlafaxine (average daily dose of 222 mg) and placebo groups, although the percentage of individuals achieving remission (defined as the proportion of patients who showed a 30% decrease in the 17-item CAPS score) was greater for the venlafaxine group (43% versus 28%). Data from this study was later analyzed for potential benefits on resilience, as measured by the Connor-Davidson Resilience Scale. [99] Resilience as measured on this scale was improved with an effect size of 0.35 for the full scale. Similar beneficial results were found when venlafaxine (N = 179; average maximum dose of 225 mg daily) was compared to sertraline (N =175; average maximum dose of 151 mg daily) and placebo (N= 179) in a 12-week, flexible dose trial. [100]

The most recent similar antidepressant tested for efficacy in PTSD is duloxetine (generally described as a serotonin and norepinephrine reuptake inhibitor; SNRI). In the first duloxetine trial, participants were given oral duloxetine as monotherapy for an 8-week open-label study beginning at 30 mg and increasing in 1-2 week intervals up to 120 mg daily. Duloxetine decreased the PCL-Civilian scores by 25% from baseline at week 8 ($t=7.0$, $p<.001$). [101] Side effects of increased dream activity (without nightmares), sleep disturbance, and increased fatigability were quite common (>50%). In a second 12-week, open-label trial, duloxetine (average daily dose = 81 mg) was tested in 20 patients. [102] All subjects had a CAPS score of at least 60 at baseline, and 15 completed 12 weeks of treatment. Of the 5 that dropped-out, 3 did so due to side effects. Significant improvements were seen on CAPS total and all subscale scores, as well as depression and sleep measures. Based on the a priori definition of a 20% or greater

improvement on CAPS total score (a relatively low threshold in comparison to most studies that set the threshold at 30-50% improvement) 9 participants (45%) were classified as responders.

In an interesting attempt to determine if duloxetine would have especially unique effectiveness based its selective norepinephrine reuptake inhibition, participants completed a fear conditioning procedure at baseline. [103] A significant reduction in symptom severity scores as assessed by the PCL-Military was seen after 8 weeks of duloxetine treatment for the individuals that demonstrated fear conditioning, but not for those that could not develop fear conditioning. Unfortunately, at this time the same paradigm has not been studied with other antidepressants; and, therefore, it is unclear how selective this conditioning paradigm is in identifying those likely to respond to an SSRI or SNRI. However, these studies suggest that duloxetine like other compounds with significant SSRI activity likely will prove to be an effective treatment.

The site of action of SSRIs was investigated in a positron emission tomography (PET) study using ^{15}O-H_2O. [104] In this pilot study characterizing treatment response to the use of paroxetine in un-medicated patients with PTSD received either paroxetine (N=7) was administered beginning at 12.5 mg daily up to 62.5 mg daily or placebo (N=6) in a double-blind fashion over a 12-week period. Participants were asked to provide a written description of their traumatic event (individuals exposed to multiple events were asked to write about the event that was the most distressing), which was then separated into two parts. Each part was 30 seconds in length, and was recorded in a neutral tone of voice by a study researcher, to be played back during scanning. Four scans were completed during each session, two with neutral scripts and two with their traumatic scripts. Regional blood flow was compared for traumatic minus neutral script conditions; these analyses were performed for pre- and post-treatment scans for both paroxetine CR and placebo groups. Pre- and post-double-blind treatment CAPS scores were compared for

paroxetine CR- and placebo-treated participants through use of repeated measures analysis of variance, with time as the repeated measure, to examine time by group interactions. Both conditions resulted in significant improvements in the total CAPS (paroxetine resulted in a 69% reduction and placebo a 61% reduction), although the percentage improvement was not statistically significant ($F=3.4$, $p=.09$). Treatment with either placebo or paroxetine was associated with increased blood flow in the anterior cingulate cortex in response to post-trauma scripts. However, paroxetine was associated with an additional increase in activity in the orbital frontal cortex. While these data are intriguing, the fact that the functional treatment response did not differ between the paroxetine and placebo groups makes it more difficult to assign significance to these findings.

(2) Non-SSRI Antidepressants

(a) Tricyclic Antidepressants

Tricyclic antidepressants were the mainstay of psychiatric care during the early years of characterization of the diagnosis of PTSD. Two open-label trials of tricyclics were published before any double-blind trials were initiated. In the first open-label report, imipramine was given to 10 consecutive private patients with PTSD (the origin of which was not described in the manuscript). [105] Doses ranged from 50-350 mg daily with an average of 260 mg daily. Patients were rated using the Impact of Event Scale (IES; note that other PTSD symptom evaluation scales were not available at the time of this study) by the treating psychiatrist. Most reported improvement of the intrusion symptoms. The second study of the use of tricyclic antidepressants used a retrospective evaluation of treatment response using the CGI Scale in 17 combat veterans. [106] In this study, 82% were much improved after 6-8 weeks of treatment. Blood levels of the tricyclics were not obtained, however. In the first double-blind, placebo-controlled, crossover

design of desipramine (average maximum dose of 165 mg daily), benefit was not observed. [107] Unfortunately, desipramine blood levels averaged only 107 ng/ml, generally lower than the levels expected to provide a high likelihood of response in the treatment of depression. In addition, treatment duration was only 4 weeks before the crossover, which may not be a sufficient duration for adequate evaluation.

The largest tricyclic antidepressant trial was an 8-week, double-blind, placebo-controlled trial of amitriptyline (average final dose of 169 mg daily) primarily in Vietnam era combat veterans (total N=46). [108] Significant benefit was identified only in the analysis of the 8-week completers on the IES. Interestingly, the blood levels reported for the amitriptyline group were higher than would be expected for the doses used (amitriptyline 211 + nortriptyline 257 ng/ml). The minimal response could also be related to the limited duration of treatment. In a case series of patients treated with a variety of psychotropics, those with a favorable response to amitriptyline sometimes required treatment periods of up to 6 months. [109] These few studies are sufficient to demonstrate that as a class tricyclic antidepressants belong in the pharmacologic armamentarium for PTSD.

(b) Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) are antidepressants that have benefit by inactivating the enzyme monoamine oxidase, partially responsible for the metabolism of norepinephrine and serotonin. An early double-blind, placebo-controlled 8-week comparison of the irreversible MAOI phenelzine (average maximum dose of 67 mg daily; N = 19) versus imipramine (average maximum dose of 225 mg daily; N = 23) in Vietnam veterans demonstrated phenelzine was superior to both imipramine and placebo (N = 18). [110] In this study, careful attention was given to ensure that there was greater than 85% MAO inhibition and that imipramine + desipramine blood

levels were greater than 150 ng/ml, indicating that both drugs were administered in adequate doses. In a later study, the reversible MAOI brofaromine was tested in a 12-week trial conducted at 12 centers throughout the country, utilizing a randomized, double-blind, flexible dose design with two parallel groups (total N = 114). [76] Although the placebo response rate was over 30%, there was no distinction in outcome on the CAPS between brofaromine and placebo. Similar results were found in a smaller study, although in the second study the CGI scores favored brofaromine. [111] Based upon these studies, it appears that in contrast to reversible MAOIs, irreversible MAOIs may have benefit. However, their utility is severely limited by the complexity of their administration induced by serious drug-drug interactions and dietary restrictions.

(c) Miscellaneous Antidepressants

Other antidepressants have also demonstrated likely efficacy, but large double-blind, placebo-controlled trials are lacking. Nefazodone, a serotonin uptake inhibitor and serotonin-2 blocker, was effective in open-label clinical trials in both civilians and veterans. [112] For example, in an analysis of the use of nefazodone at 6 sites in a total of 105 patients, demonstrated that nearly half (46%) experienced a 30% improvement in the outcome measure (usually CAPS). Nefazodone was well tolerated. Younger patients were more likely to respond to treatment, as were non-combat-trauma patients.

Two open-label trials and a small placebo-controlled trial, suggest use of mirtazapine is helpful. [113,114,115] In open label studies associated with small sample sizes, modest benefits were demonstrated that increased further with treatment up to 24 weeks. [113,114] In the controlled trial, patients were titrated to a maximum 45 mg mirtazapine dose daily in an 8-week trial. [115] Significantly more individuals treated with mirtazapine (79%; N = 17) than placebo (17%; N =

9) demonstrated improvement on the Short PTSD Rating Interview (SPRINT) (response was defined as a score of very much improved or much improved). Unfortunately, definitive large-scale trials have not been performed.

Despite the longstanding propensity of clinicians to prescribe trazodone for insomnia and its known antidepressant efficacy, there have not been any controlled trials of its use for treatment of PTSD. A very small open-label trial in Vietnam veterans with combat-related PTSD (N =6) demonstrated only modest (<25% decreases in CAPS-2) over 4 months. [116] It is unknown whether the dosage used (maximum of 400 mg daily) was sufficient for treatment of the core symptoms of PTSD. In addition, a study of the use of trazodone for insomnia in combat veterans demonstrated that of those that tolerated it (81%), most had significant improvement in both insomnia (92% noted improvement in sleep onset and 78% reported improvement in sleep maintenance) and decreased frequency of nightmares (72%). [36] Further characterization of trazodone's effects on the primary symptoms complexes of PTSD is needed, however.

Results of the one controlled trial of bupropion for treatment of PTSD were not promising. [117] In this small double-blind, placebo-controlled, flexible dose 8-week trial, participants were gradually increased to the maximum tolerated dose or 300 mg daily while remaining on their currently prescribed antidepressant (if the dosage remained stable). No difference in total CAPS scores was seen between the bupropion (mean decrease from baseline = 12; N = 18) and placebo (mean decrease from baseline = 17; N = 10). The most positive outcome was that patients tolerated bupropion well. The use of a very chronic veteran population and a limited dosage range for bupropion in this trial make it very difficult to be sure that an adequate trial occurred, and no subsequent studies have been published.

(5) Anticonvulsants

It is common for anticonvulsants to be evaluated for their benefits in the management of psychiatric conditions. The management of PTSD has also been a focus of clinical trials with anticonvulsants. The results of these clinical trials have been mixed; and, consequently, some authors and guidelines suggest anticonvulsants offer little or no benefit [8] (also, http://www.healthquality.va.gov/Post_Traumatic_Stress_Disorder_PTSD.asp, 2010). Such a generalization reflects the general lack of adequately powered controlled trials. In contrast, several reports provide justification for consideration of anticonvulsants in the pharmacotherapy of PTSD; although, most are small, uncontrolled studies leaving obvious unanswered questions about efficacy. For example, in one case report a patient with non-combat PTSD that was not responding to escitalopram (30 mg daily) plus quetiapine (150 mg daily) began responding when pregabalin at 225 mg was added. [118] A subsequent open-label trial of adjunctive use of pregabalin in nine patients on stable doses antidepressants corroborated the likely benefit of pregabalin. [119] Controlled trials have not been published, however. In this section the results of clinical trials with tiagabine, oxcarbazepine, gabapentin, levetiracetam, topiramate, and valproic acid are discussed. The available evidence suggests that valproic acid and tiagabine are unlikely to provide clinical benefit. There is insufficient evidence to conclude that oxcarbazepine, gabapentin, levetiracetam or topiramate are effective. The strongest evidence for potential efficacy of an anticonvulsant was found with topiramate.

A review of the literature on the pharmacotherapy of PTSD with anticonvulsants would not be complete without discussing the use of valproic acid, which has been the most often used anticonvulsant in psychiatry. Its use in PTSD began with an open-label trial as adjunctive therapy in 16 mostly Vietnam-era veterans who were monitored over an average of 11 months with an average dose of 1086 mg daily and an average plasma level of 70 ug/ml. [120] Symptoms

were evaluated on a four-point scale (0=none, 1=mild, 2=moderate, and 3=severe) for each of the three main symptom clusters (re-experiencing, hyperarousal/hyperreactivity, and avoidant). Most participants (10 of 16) appeared to demonstrate improvement. As a result of treatment, some were able to discontinue concomitant medications. In a second similar trial in mostly Vietnam-era veterans, a statistically significant, but hardly a clinically significant 18% drop in the total CAPS score at 8 weeks was observed. [121] The total daily dose averaged 1365 mg (range from 1000 to 2500), and valproic acid plasma levels averaged 80 ug/ml (range from 53 to 107). Similar findings occurred in a case series of 7 individuals with PTSD resulting from childhood sexual abuse treated for 8 weeks. [122] In this study there was a 40% drop in the PTSD Symptoms Scale–Self Report scale after the addition of an average of 1500 mg daily of valproic acid. The largest open-label trial of valproic acid involved 30 combat veterans who were given monotherapy with valproic acid. [123] In this trial the average dose was 1840 mg daily and the average blood level was 69 ug/ml. A 30% drop in the total CAPS score was observed in the 14 patients that completed the 8-week trial. A meta-analysis of the published trials suggested that the use of valproic acid results in limited benefits and clearly needed a randomized, double-blind trial to provide clarity on its efficacy. [124] Such a trial was published the following year involving 85 veterans with mostly combat-related PTSD. [125] In this 8-week trial, the baseline and week 8 total CAPS scores were nearly identical for both the valproic acid and placebo groups. The average divalproex dose was 2309 mg daily by week 8 with a mean serum valproic acid level of 83 ug/ml. These studies cast doubt on the likelihood that valproic acid is of benefit in the treatment of PTSD, particularly for a chronically ill population with combat-related PTSD.

Tiagabine was first tried as an adjunctive treatment for PTSD in a patient that had not responded to venlafaxine at 225 mg daily. [126] Intrusive thoughts and nightmares diminished

only after the addition of tiagabine (8 mg daily). A subsequent open-label trial in seven women that remained symptomatic despite ongoing antidepressant medications demonstrated a 34% decrease in the PTSD Symptom Checklist (PCL) - Civilian total score using a mean effective dose of 8 mg (range 4-12 mg). [127] A second open-label trial with tiagabine enrolled 29 participants, of which 19 completed the 12-week open-label treatment phase. [128] The 18 participants that demonstrated improvement were enrolled in a second 12-week, double-blind, placebo-controlled treatment withdrawal phase. In the initial phase of the study there was clear improvement as measured by the primary outcome measure, the SPRINT. Discontinuation of the tiagabine in the second 12-week phase did not result in clinical deterioration, however. Consistent with antidepressant trials, those participants that remained on tiagabine were more likely to show continued improvement. The most definitive evaluation of the efficacy of tiagabine was a double-blind, placebo-controlled, multi-center trial in 232 participants equally divided between tiagabine (N=116) and placebo (N=116). [129] In this study the tiagabine was given as monotherapy in increasing doses up to 16 mg daily (average 11 mg). Baseline CAPS total scores were 82 and 83 for the tiagabine and placebo groups, respectively. Both groups had a 30-point drop in total CAPS scores after the 12-week trial, and therefore tiagabine did not out perform placebo. However, it is difficult to fully understand the significance of these findings when there was such a dramatic placebo response. Tiagabine was well tolerated in all studies with the primary side effects adverse events after tiagabine versus placebo being dizziness (32% vs. 13%), headache (25% vs. 27%), somnolence (20% vs. 10%), and nausea (18% vs. 20%). Further trials are required to fully characterize the clinical utility of tiagabine in management of PTSD, especially in long-term use.

Case reports involving a total of four individuals demonstrate that there is a potential for the

use of oxcarbazepine for management of PTSD. An initial report of the use of oxcarbazepine showed benefit when it was added at 450 mg twice daily to a combination of sertraline 150 mg daily and clonazepam 0.5 mg twice daily. [130] A subsequent report in a woman that experienced both PTSD and bipolar disorder again demonstrated the possibility of improvement with oxcarbazepine monotherapy (750 mg twice daily). [131] Two other individuals were treated with oxcarbazepine monotherapy with reported benefit, which was introduced as part of an alcohol detoxification paradigm (600-1200 mg daily). [132] Controlled trials are not available, however.

Gabapentin has often been tested for the treatment of psychiatric conditions. Case reports indicate that the addition of gabapentin to antidepressant therapy markedly improved the clinical response, including decreased nightmares and improved functionality. [133,134] In a retrospective review, 30 Vietnam-era veterans who received adjunctive gabapentin (average dose of 1190 mg daily) were judged to have mild to moderate improvement. [135] Those on higher average doses (1344 mg daily) generally had a better response than those on lower doses. Despite these promising results, there are no double-blind, placebo-controlled trials in the literature.

Levetiracetam is infrequently used an intervention for psychiatric conditions, but was evaluated in a retrospective review of 23 patients with PTSD resulting from a variety of traumatic events and only partial- or non-responders to their antidepressant therapy. [136] Addition of levetiracetam (average dose of 1967 mg daily, usually divided doses) for an average of 10 days resulted in a 23% decrease in the PCL-Civilian version (Baseline mean of 67 to endpoint mean of 44). However, controlled trials have not been published.

Topiramate is an anticonvulsant that has been the focus of multiple trials in a variety of psychiatric conditions. It was initially tried as adjunctive therapy in 3 patients with non-combat PTSD. [137] The patients in this report all demonstrated benefit from low (37.5 mg daily) to high

doses (600 mg daily), and the benefits remained after concomitant therapy was discontinued. The same author published a case series of 33 civilian patients followed with the PCL-Civilian. [138] In these patients topiramate as monotherapy (N=5) or as adjunctive therapy (N=28) resulted in a 30% decrease in the PCL-Civilian total score in just 4 weeks (median response of 9 days, and median dose of 50 mg daily). Most were rated as being full responders (defined as experiencing a 30% decrease in the PCL-Civilian total score) to topiramate (79%). Interestingly, 21% dropped out of the study because of adverse events, primarily overstimulation. Maintenance response was not evaluated. In an open-label trial of topiramate at up to 200 mg daily for 8 weeks in combat-related PTSD of Australian Vietnam era veterans, only a 22% decline in total CAPS scores was observed. [139] The initial double-blind, placebo-controlled monotherapy trial in 38 civilian outpatients used topiramate at starting doses of 25 mg daily that were titrated by 25-50 mg each week to a maximum dose of 400 mg daily (given in divided doses) demonstrated a 60% drop in the primary outcome measure, total CAPS scores. [140] Unfortunately, there was a 46% drop in the placebo group total CAPS scores, and the difference between the two groups was not statistically significant. One of the secondary outcome measures, TOP-8, did demonstrate some benefit (p=.025). It appears that the study was not adequately powered to definitively determine whether topiramate is helpful. A second 12-week double-blind, randomized, placebo-controlled study of topiramate involved 35 civilian outpatients in Brazil who were begun on 25 mg at bedtime and increased by 25 mg weekly, as tolerated, until the total CAPS score was 20 or below, the end of the study was reached, or until maximum dose allowed was reached (200 mg/day). [141] In this study there was a 73% decrease in the total CAPS score after 12 weeks in the completers (N=14 for topiramate group), but a 50% decrease in the total CAPS in the placebo group (N=12 for placebo group). Unfortunately, using an intent-to-treat

analysis did not demonstrate response, suggesting that this particular trial was both underpowered and did not include sufficiently high doses to demonstrate benefits. The response that was observed appeared to be strongest for the avoidance/numbing symptom cluster, however. While the results of these multiple trials are promising, the controlled trials appear to lack sufficient power to provide definitive evidence of whether topiramate is an effective pharmacotherapy for PTSD. [142] However, these studies clearly suggest that larger controlled trials with topiramate are warranted.

(6) Benzodiazepines

Because benzodiazepines are generally considered unhelpful and potentially harmful, they are on the list of compounds that are not recommended for use in the treatment of PTSD (http://www.healthquality.va.gov/Post_Traumatic_Stress_Disorder_PTSD.asp; 2010). The potential for harm is supported by an early report that demonstrated in a Vietnam combat veteran a dissociative experience occurred in response to an intravenous high dose (15 mg) of diazepam. [143] In addition, there is one report of significantly increased sensitivity to withdrawal from high doses of alprazolam in patients with PTSD. [144] Six of eight patients expressed homicidal ideation during withdrawal; however, this was not a controlled study, and it is unclear whether the vulnerability was caused by too rapid a withdrawal paradigm.

There is some evidence to suggest that the commonly held concerns about the risk associated with benzodiazepine use may be exaggerated. In a retrospective review of 370 Vietnam veterans with PTSD and substance abuse benzodiazepine use did not predict unfavorable outcomes at one year of treatment based on outcome measures including inpatient and outpatient health service utilization, severity of alcohol and illicit drug use, anxiety and PTSD symptoms, psychosocial functioning, and violence assessed at baseline and at 4-month intervals during the year following

discharge. [145] Unfortunately, the amount of benzodiazepine use was not reported making it difficult to fully assess the relationship of benzodiazepine use and behavioral responses. Also, the high potency benzodiazepine midazolam is often used in management of surgical interventions of burns. When use of midazolam was studied in 370 OEF/OIF soldiers with burns that were administered the PCL-M, 211 underwent at least one surgical intervention, and 142 received intravenous midazolam (1-5 mg). [146] Midazolam use did not affect the later incidence of PTSD, consistent with the hypothesis that benzodiazepine use in itself may not be as problematic as reported in the various guidelines about PTSD treatment. However, potential harm from benzodiazepines is difficult to predict, and may be significantly influenced by a variety of factors including current psychiatric state, presence of other medications, concurrent substance use, and withdrawal states. [147] Thus, the potential for behavioral dyscontrol with the use of benzodiazepines in PTSD should not be overlooked even though their use may not be uniformly harmful.

There were early attempts to determine whether benzodiazepines would be efficacious for the core symptoms of PTSD. The initial attempt to assess efficacy of benzodiazepines for treatment of the core symptoms of PTSD was with the use of alprazolam. [148] Alprazolam was evaluated in a double-blind, placebo-controlled, crossover design requiring 5 weeks of treatment with each condition in 10 subjects. Alprazolam was used in doses beginning at 1.5 mg daily but increased up to 6 mg daily. Observer ratings using the DSM-III PTSD diagnostic criteria did not demonstrate any benefit for alprazolam. The only alprazolam-associated benefit was a modest decrease in Hamilton Anxiety Scale scores. Despite significant dropouts and the relatively low number of participants, it is clear that there are no robust benefits to the use of benzodiazepines on the core symptoms of PTSD. In a second attempt to assess the role of the use of

benzodiazepines in management of the core symptoms of PTSD, temazepam (30 mg; N=11) or placebo (N=11) were administered at bedtime for 7 days to patients enrolled at the time of admission to an inpatient unit for management of acute stress symptoms. [149] Temazepam was effective in prolonging sleep, but showed no effect on subsequent improvement in the CAPS total scores, and the benefit only lasted as long as the temazepam was being administered. Six weeks following the initiation of treatment and five weeks after discontinuation of temazepam, there was no longer any benefit. Similarly, either alprazolam or clonazepam were tested for management of what now would be called Acute Stress Disorder in a study performed in Israel. [43] Consecutive individuals (N= 162) evaluated in an emergency department deemed requiring medications (N=13) were referred to a psychiatrist for medications (clonazepam average daily dose of 2.7 mg or alprazolam average daily dose of 2.5 mg). Treatment occurred for at least one month, although 9 patients continued treatment for 6 months. A control group of individuals that were not referred for medications was identified by matching patients on the IES from the same group of consecutive patients. The prescribing psychiatrist remained blind to evaluations. The percentage of individuals with a Structured Clinical Interview for Diagnosis (SCID) diagnosis of PTSD at 6 months did not differ between groups. The only treatment-responsive finding was that those on benzodiazepines possibly had a lower heart rate at 6 months (repeated measures ANOVA trend toward a time-by-group interaction, $F=2.71$; $df=2,44$; $p=.08$). This study is often quoted as an indication that early use of benzodiazepines is not beneficial in diminishing the onset of PTSD; however, this study has many significant shortcomings. First, those in the placebo group were not randomly selected, and may reflect some subtle systematic bias. Second, the dose of benzodiazepines was low to moderate and thus could be insufficient to provide benefits. Finally, the small sample size precludes basing firm conclusions on this data.

Consistent with the consensus that benzodiazepines lack efficacy for the treatment of the core symptoms of PTSD, the use of a benzodiazepine antagonist flumazenil administered to patients with PTSD did not induce panic episodes in two separate studies, one involving civilians [150] and another in Vietnam era combat veterans. [151] These studies suggest that the pathophysiology of anxiety associated with PTSD is significantly different from panic disorder because flumazenil administration to patients with panic disorder results in panic episodes. [152]

7. Antipsychotics

Antipsychotics have been evaluated mostly in relatively small, uncontrolled studies, but generally these studies demonstrated benefit to their use. There is very limited information available in the psychiatric literature on the treatment of PTSD with first generation antipsychotics. Only one case report was found of the use of thioridazine in non-psychotic PTSD. [153] In this case a man hospitalized for stabilization because he was increasingly irritable at home, improved when thioridazine (50 mg four times daily) was administered. Other medications (trazodone and diazepam) were systematically tapered until they were discontinued. Formal structured assessment of the PTSD symptoms did not occur, but the patient reported resolution of nightmares and anxiety symptoms. The benefits of the use of thioridazine in this case report should not be surprising because the benefits demonstrated in second-generation antipsychotics are usually also present for first generation antipsychotics.

The second-generation antipsychotics olanzapine and risperidone have both demonstrated some benefit in controlling the symptoms of PTSD in small controlled trials, [8,154,155] Pae et al. [154] performed a meta-analysis of seven small randomized, double-blind, placebo-controlled trials (combined N for all seven trials was 177) evaluating the efficacy and safety of olanzapine and risperidone. Included in this analysis were monotherapy and adjunctive therapy studies, although

most studies were adjunctive. A standardized mean difference in the total CAPS between the antipsychotic and placebo groups was -0.45, which would be considered a moderate effect. In general, the second-generation antipsychotics were well tolerated in these trials.

In contrast, results from a large VA multi-center, double-blind, placebo-controlled trial (supported by the VA Cooperative Studies Program) of adjunctive risperidone (average daily dose of 2.7 mg) that included 296 randomized participants has just been published. [156] There were no overall benefits identified to adding risperidone as measured by the total CAPS in this study (X difference from placebo of 2.7, p=.12). However, both re-experiencing (X difference from placebo of 2.0, p=.004) and hyperarousal (X difference from placebo of 1.7, p=.005) symptom complexes did have modest but statistically significant responses to risperidone. It should be noted that this study was performed in a very chronically ill group with approximately two-thirds receiving disability payments for their condition. Any positive findings in such a group warrants acknowledgement.

Quetiapine, a third second-generation antipsychotic, was first tried as an adjunctive to paroxetine. [157] In a single case of non-combat PTSD a patient not responding to paroxetine alone at 40 mg daily, began responding with the addition of quetiapine at 150 mg daily. Subsequently, two trials in Vietnam veterans with combat-related PTSD demonstrated some benefit of addition of quetiapine. [158,159] In the first trial, 18 of 20 Vietnam veterans completed 6 weeks of open-label treatment with an average dose of 100 mg daily (range 25-300 mg) showed a 25% improvement in CAPS scores (90 at baseline to 68 at week 6). [158] General psychopathology (PANSS) and depressive symptoms were also reduced at the 6-week end point. Similar results were identified in a retrospective review of 125 Vietnam veterans with PTSD, although only a clinical impression of improvement as reflected in the medical record was used as the endpoint

in this study. [159] There are no double-blind, placebo-controlled trials available for evaluation of the efficacy of quetiapine in PTSD.

There is one report of two cases where ziprasidone was initially added to ongoing treatment and then all other pharmacotherapies, except for low dose trazodone for sleep, were discontinued successfully. [160] A double-blind, placebo-controlled trial was initiated with a combination of sertraline (up to 100 mg daily) with ziprasidone (up to 160 mg daily). [161] The trial was interrupted after only 7 enrollees because all of the ziprasidone-treated participants had significant side effects (nausea, headache, trembling, dizziness, vertigo, impaired vision, rigidity in the jaws, diarrhea, fatigue, and impeded micturition) within the first two weeks. It is unclear whether these effects resulted because of the simultaneous initiation of the sertraline and ziprasidone. It is unknown whether ziprasidone alone would be sufficient for benefit.

(8) Placebo Response Rate for PTSD Treatment Trials

Interestingly, the placebo response rate for PTSD is generally of the same magnitude of that for treatment of depression, approximately one-third. [7,8,77,78,79,81,82,88,98] For example, in one study of treatment of PTSD with venlafaxine, remission rates of 50% were achieved with venlafaxine and placebo remission rates were 37%. In another study from the same group, placebo remission rates with sertraline (defined as a DTS score <18 or CAPS< 20) were approximately 15%. [162] Unfortunately, as described above in the sections recounting clinical trials of various psychotropic classes, higher placebo rates are sometimes seen in clinical trials, confounding evaluation of the efficacy of novel agents. [104,129,141]

(10) Limitations of Published Treatment Trials

Based upon the studies described above, there are obvious limitations to current published trials of agents to treat PTSD. First, they are characterized by small sample sizes. Second, most

are single drug comparisons to placebo; that is, there is no active comparator. Third, the trials have almost exclusively used fixed doses or at most very limited dosage ranges. Fourth, studies of combat-related PTSD have focused on very chronically ill individuals. Fifth, very few studies have included psychotherapy treatment groups for comparison. Finally, management of co-morbid conditions has not been generally addressed.

Based on these limitations it is not surprising that a meta-analysis of antidepressant trials for management of PTSD shows only very modest improvements. [48] Specifically, SSRIs and other antidepressants show on average only a 5-6 point Clinician Administered PTSD Scale improvement (<10%) over placebo. This clearly is a small effect size (Cohen's D <0.2). A partial explanation for the fact that effect sizes in antidepressant trials has been lower than seen in psychotherapy trials was provided in a recent commentary by Hoge who pointed out that "effect sizes in randomized controlled trials of SSRIs or SNRIs have generally been lower than those in psychotherapy trials, but this is likely due to the higher efficacy of placebo controls in double-blind studies than wait-list conditions in psychotherapy trials". [163]

It is not surprising, then, that the Institute of Medicine in their recent report "Treatment of PTSD: An Assessment of the Evidence" (http://www.nap.edu/catalog.php?record_id=11955; 2007) concluded that the current evidence does not support conclusions about the potential benefits of any pharmacologic category. Their report added concerns that pharmaceutical manufacturers funded the majority of drug studies. They added that there existed significant gaps in assessing the efficacy in subpopulations such as those with co-morbid conditions. Finally, they concluded that: (1) current research was inadequate to answer questions about interventions, settings and lengths of treatment; (2) studies have not systematically addressed efficacy and comparative effectiveness of treatments in clinical use; (3) there is no generally

accepted definition for recovery in PTSD; and (4) the current evidence does not allow us to determine the value of early interventions.

The Institute of Medicine recommended the use of methods with increased internal validity and standardization of treatment with the Veterans Administration taking the lead for studying combat-related PTSD. They added that future research should focus on the evaluation of comparisons of psychotherapy and medications, as well as evaluation of the efficacy of combined psychotherapy and medication. Finally, their report suggested that further studies on early interventions after traumatic exposure should be supported.

(11) Factors Predicting Response to Pharmacotherapy

Despite the wealth of information summarized above describing response to antidepressants and other classes of psychotropics, to date there is limited information available regarding the determinants of antidepressant response in patients with PTSD. One opportunity to learn about factors that are likely to be important in the alleviation of the symptoms of PTSD is to understand the determinants of response to antidepressants in patients with major depressive disorder because, in general, antidepressants are of benefit for both disorders. There are multiple studies that have explored the psychosocial and clinical factors that influence response to antidepressant therapy in patients with a diagnosis of depression. [164] Some demographic factors, including age, gender, race, ethnicity and age appear to have minimal if any effects on antidepressant response. [165] However, living with a significant other, establishing long-term relationships, a higher educational level, a higher baseline quality of life, and a greater intrinsic religious focus are predictive of better treatment response in patients with depression. [166,167]

Of the several clinical determinants of antidepressant response that have been characterized, the presence of an early response to antidepressants is one of the most important predictors of

satisfactory treatment response over the first few months. [168,169] Conversely, lack of response in the first two weeks increases the likelihood of a poor outcome at week eight. Also, there appears to be an inverse relationship between the severity of depressive symptoms and treatment response, at least for the primary depressive episode. [170]

Another important clinical factor influencing treatment response is the presence of cognitive impairment. Depressed patients with cognitive impairment are less likely to respond to antidepressant therapy. [165,171] This factor, in particular, may be important to consider for predicting the likelihood of recent veterans' treatment response in combat-related PTSD because of the significant risk of head injury associated with the unique frequency of blast injuries experienced in the Iraq conflict. Similarly, most studies demonstrate that co-morbid anxiety disorders predict poorer response to antidepressant therapy. [172,173]

Based on the findings discussed above on antidepressant response in depressed individuals, it appears that the most likely factors to influence treatment response in PTSD will be: (1) the adequacy of social supports, (2) the magnitude of early response to treatment, (3) the baseline severity of PTSD and (4) the degree of cognitive impairment present. In fact, the limited studies evaluating factors associated with pharmacological response in chronic PTSD support these conclusions. In addition, one report based upon data from two separate clinical trials suggests that anger response and the presence of peritraumatic tonic immobility (PTI) are also helpful in predicting the likelihood of treatment response. [174,175]

There have only been four studies that directly address factors that would predict response to treatment in PTSD. [174,175,176,177] In the first study addressing factors predicting pharmacological response, 55 individuals were treated in a double-blind, placebo-controlled trial with amitriptyline and drug response was rated based upon the CGI-Improvement. Those rated as

much improved or very much improved were identified as responders. Multivariate logistic regression analyses were used to predict CGI outcome. Using this method, drug response was associated with lower baseline levels of depression, neuroticism, or anxiety. Similarly, when IES was used as the outcome measure, the lower baseline depression scores, lower current PTSD scores, and lower levels of combat intensity correlated with higher response rates. In the second study, treatment response to brofaromine was predicted by lower baseline score on the total CAPS, and the CAPS re-experiencing and avoidance/numbing subscales, consistent with the concept that greater symptom severity predicts a lower response rate. [177] Using data from two previously published studies, Davidson, et al. evaluated the predictive power of the anger item (No. 14) on the Davidson Trauma Scale (DTS). [174] The total frequency (0–4) and severity (0–4) scores for item 14 on the DTS were summed to assess anger. In the 318 patients evaluated, the anger item score change from baseline to the end of week one predicted those likely to demonstrate a positive response at week 12. An increase in anger of 30% at one-week best predicted the likelihood of non-response to treatment in both the drug and placebo groups. Complete resolution of anger at week one was associated with a 23% decline in the overall PTSD score (score with the anger item deleted) at endpoint.

More recently, a novel factor, peritraumatic tonic immobility (PTI), was evaluated in 23 patients who had experienced urban violence. [175] An independent evaluator determined a score on the Tonic Immobility Scale, which is a 10-item scale addressing 2 factors: tonic immobility and fear. PTI was present in 43% of this group. Those with who met criteria for the presence of PTI were much less likely to demonstrate responsiveness to antidepressant therapy. That is, 1 of 10 with PTI had a PCL-Civilian less than 50 at the end of treatment, while 7 of 13 without PTI met that criterion of response.

4. Drug Choice, Dosage and Duration of Treatment

The consensus of most reviews is that SSRIs remain the first choice for pharmacological management of chronic PTSD. [48] In fact, the use of SSRIs is the only pharmacotherapy that is highly recommended by the 2010 VA/DoD Clinical Practice Guidelines. Consistent with these recommendations, two SSRIs have received recognition by the Food and Drug Administration (FDA) as indicated for treatment of PTSD, sertraline and paroxetine. There currently is no method of determining which SSRI will be effective for any one individual or whether an individual is unlikely to respond to an SSRI.

SSRIs would be expected to be effective for amelioration of the symptoms of PTSD based upon their direct effects to increase brain serotonin availability, and consequently their ability to suppress noradrenergic activity in the locus coeruleus. [22] In fact, indirect evidence for a beneficial effect of increased serotonergic activity is seen in a recent study showing that acute tryptophan depletion (decreases the serotonergic accumulation) causes a reemergence of PTSD symptoms in patients that had been stabilized on SSRIs. [178]

Characterization of the requirement of a sufficient antidepressant dosage is not well documented in the PTSD literature. Whether fixed dosage or flexible dosing strategies have been used, the dosage range has been limited to no higher than moderate ranges. [7,48] It is likely that the restricted dosage ranges are influenced by the wish to remain within accepted FDA-approved guidelines. However, there has not been an attempt to determine if there is any added benefit can be gained by systematically increasing the dosage to the maximum tolerated in individual patients.

Most studies of pharmacological treatment of PTSD have been no longer than 12 weeks in duration. [7,48,97] However, when longer treatment durations are used, the response to treatment

appears to increase. For example, in a case series with amitriptyline response improved with treatment up to 6 months. [109] The most definitive evidence comes from a study of the effectiveness of sertraline in which 188 patients who completed 12 weeks of a double- blind, placebo-controlled, acute-phase treatment for PTSD with sertraline were further treated in a 24-week open-label continuation phase. [97] Efficacy measures included the CAPS-2 severity score, the IES, and the CGI-Improvement and -Severity of Illness scales. Treatment response was defined as >= 30% decrease in the CAPS-2 total severity score (compared with acute-phase baseline score) and a CGI-Improvement score of 1 or 2. In this 24-week open-label continuation of treatment phase, 92% of acute-phase responders maintained their response during the full 6 months of continuation treatment and 54% of the non-responders became responders. In addition, a significant portion of the total response to sertraline (20-25%) occurred during the 24-week continuation phase. Consistent with other studies, the greater the severity of symptoms on the CAPS-2, the longer time to response, and a greater likelihood that response occurred during continuing phase treatment. This study strongly suggests that treatment of chronic PTSD may require longer pharmacotherapy duration than necessary for management of depression. However, systematic study of the treatment duration required for remission has not been published.

4. Does Treatment Need to Vary Based Upon the Etiology of the PTSD?

There have not been any systematic attempts to compare treatment responses to pharmacotherapy in individuals who developed PTSD following a single traumatic event versus chronic traumatic exposures. Most pharmacotherapy trials have been performed in civilians with varied trauma exposure, but mostly based upon exposure to single traumatic events. While the possibility that civilians with PTSD may be more responsive to treatment than combat veterans

has been entertained; [1,88,96,179] based on the available data, it is difficult to make fair comparisons between the two population groups. For example, when the pharmacologic management of combat-related PTSD has been addressed, it has most often been in Vietnam-era U.S. veterans over 30 years after the onset of their PTSD symptoms, whereas the management of non-combat PTSD in civilians is usually associated with much less chronic symptomatology. Understandably, to date pharmacologic approaches studies focusing on combat-related PTSD have shown mixed results. Two small open-label studies, one in World War II Dutch resistance fighters and one in Vietnam veterans, using fluvoxamine (N=22 between the two studies) suggested efficacy of SSRIs in the treatment of chronic combat-related PTSD. [83,180] Unfortunately, three trials in Vietnam veterans, a small double-blind trial with fluoxetine with a maximum average dose of 48 mg daily at 12 weeks (N=12), [179] and two larger trials of sertraline were negative. [88,181] In 2002 a study was conducted in Israel, involving mostly combat veterans (86%) with PTSD who were randomly assigned to a 10-week, flexible-dose, placebo-controlled trial. [181] Participants were randomly assigned to sertraline (N = 23) or placebo (N = 19). Of completers in this trial, sertraline treated participants were more likely to have a 30% reduction in the total CAPS-2 score, have a CGI Score of 1 or 2, or experience both findings. The findings were not significant for an intent-to-treat analysis, however, suggesting that the study did not have sufficient power based on the number of enrollees. In a second study, [88] only U.S. veterans were evaluated in a multi-center, 12-week, double-blind, flexible dose trial. Sertraline (N = 86; average daily dose of 135 mg) did not produce a greater change in the CAPS-2 than placebo (N = 83; average daily dose of 172 mg). The negative results could have been influenced by the choice of low to moderate dosing.

Despite these disappointing early results, two studies in the past decade suggest that combat-related PTSD may be responsive to the SSRI fluoxetine. [81,82] In the first study, performed in subjects from various war-torn countries in Europe, Israel and South Africa, 48% had relatively recent exposure to war violence as the source of their PTSD symptoms. Fluoxetine was shown in this trial to promote improvements in the primary outcome measure, the TOP-8, as well as various secondary measures (CAPS) and various standard measures of anxiety and depression. Similarly, fluoxetine was found to be effective in a 12-week, flexible dose, placebo-controlled trial treating the symptoms of PTSD resulting from combat-related trauma in patients (N = 144) from Bosnia-Herzegovina, Croatia, and Yugoslavia. [82] Fluoxetine (N=110) treated patients had greater improvements in the TOP-8 and total CAPS-2 scores than for those receiving placebo (N=34), with fluoxetine to placebo differences of 4 and 15 points, respectively. There was also clinically significant improvement in the SF-36 mental health items (15 points improvement over placebo).

The number of such studies in recent combat veterans is limited and further work is obviously necessary to be certain of the benefits in this population. However, the results suggest that recent-onset, combat-related PTSD may be as responsive to SSRIs as other cases of PTSD. These studies suggest that the chronicity of the syndrome is more important than etiology in determining whether treatment resistance is likely.

5. Use of Augmenting Agents

There is an abundant literature looking at possible strategies for augmentation of antidepressant response in the treatment of PTSD, and those studies have been described above. Possible adjunctive medications include: prazosin, first or second-generation antipsychotics, tricyclic antidepressants, trazodone, non-SSRI antidepressants, buspirone, and some

anticonvulsants. The best data is available for the use of prazosin, second-generation antipsychotics, and trazodone. Although algorithms have been proposed, they have not been empirically tested. In fact, there are no controlled comparisons of augmenting strategies for pharmacological management of PTSD. With this in mind, it is logical to keep in mind that the current pharmacotherapy of PTSD appears to parallel the treatment of depression. Focusing on augmenting strategies used for treatment of depression will likely provide an improved understanding of possible approaches to the use of augmenting agents in the treatment of PTSD.

It should be noted that the more severe cases of PTSD may be associated with psychotic features. When these are present, antipsychotic medications are warranted.

6. Maintenance Treatment and the Prevention of Relapse

There are limited data that address the issue of how long treatment duration should be for maintenance of remission from PTSD. It is clear from multiple studies that maintenance treatment is superior to acute treatment only. [87,92] In a study of maintenance treatment with fluoxetine, 131 patients that responded to fluoxetine during a double-blind trial either continued on fluoxetine (N=69) or were switched to placebo (N=62). [92] The average fluoxetine dose was 57 mg during the maintenance period. A time to relapse analysis showed that fluoxetine was superior to placebo in relapse prevention (log-rank X^2=4.88, p=.027). Being switched to placebo resulted in worsening of the CAPS avoidance score (F=5.44, p=.02), and CGI Severity score (F=8.39, p=.005). The CAPS total score was just outside statistical significance (F=3.80, p=.054).

In another study of relapse prevention, 96 patients were randomly assigned to a double-blind design of 28 weeks of maintenance treatment with sertraline (50–200 mg, mean dose at endpoint of 137 mg; N=46) or placebo (N=50). [87] Patients received biweekly assessments with the CAPS,

the IES, and the CGI Severity and Improvement ratings. Continued treatment with sertraline resulted in lower PTSD relapse rates than placebo (5% versus 26%), as well as a many fold (6.4 X) decrease in likelihood of relapse. Sertraline's benefits did not differ across the three core PTSD symptom clusters (re-experiencing/intrusion, avoidance/numbing, and hyperarousal). Those with early response to acute treatment were less likely to relapse after placebo substitution.

These studies clearly demonstrate the benefits of continued use of SSRIs when there is response. What is not known is the total duration of treatment that is required to prevent relapse. There have not been any studies published that directly address this issue. A prudent clinical guideline would suggest that treatment should continue until full remission has been present at least one year, and likely longer.

B. Treatment of Traumatic Brain Injury (TBI)

1. Overview

Traumatic brain injuries (TBIs) are the leading cause of traumatic death and long-term disability in the United States, affecting approximately 1.5 million individuals annually. [182] Approximately 6% (90,000) of those with TBIs annually will experience long-term disability from their injury. These statistics capture those that have been hospitalized as a result of their injury and subsequently exhibit a disabling condition. The long-term effects of more subtle injuries are less well characterized. However, there are data that suggest that as the individual with a significant TBI ages there are declines in physical and cognitive functioning, as well as societal participation. [183] There are no data to inform us on whether it is possible to affect the long-term course of TBI with pharmacological intervention. However, there is a significant

literature describing attempts to pharmacologically manage the cognitive and behavioral sequelae of TBI. [10,11,12]

The current U.S. conflicts in Afghanistan and Iraq have resulted in a significant incidence of TBI. [184] If the criterion of head injury with associated loss of consciousness is used the estimated prevalence is 5%. If the more liberal criterion of head injury with any associated alteration of mental state the prevalence could be as high as 10%. In cases of mild TBI in civilian populations, overt symptoms may resolve within days or weeks of the injury. [185] However, nearly half (up to 40%) may have persistent symptoms. [186,187] A significant percentage of individuals with TBI also experience PTSD. In fact, for individuals in the recent OEF/OIF conflicts, over 40% of those with head injury associated with loss of consciousness had both TBI and PTSD. [184]

The pharmacologic management of traumatic brain injury (TBI) is even more complex than the management of PTSD because, unlike PTSD, TBI is associated with a substrate of often multiple brain regions contributing to the behavioral dysfunction.

The pathophysiology of TBI has been reviewed by Werner and Engelhard. [188] Conceptually, there are two principal mechanisms for development of the primary insult of TBI: (1) focal brain damage resulting from the contact injury, and (2) diffuse brain damage due to immediate mechanical/acceleration-deceleration injury associated with diffuse axonal injury or brain edema. [188] The secondary insult of TBI results from the multiplicity of physiologic processes that occur post injury. [188,189] The primary insult can only be limited by preventative measures. However, the various secondary injury processes including that lead to apoptosis are the most likely targets for pharmacological intervention. Werner and Engelhard [188] summarize these pathophysiologic processes that result in the progression of the secondary insult. It is beyond the scope of this

review to reiterate details of the pathophysiologic processes. However, characterization of these processes makes it clear that there are theoretically multiple possible junctures at which pharmacological interventions would be of benefit include: reinstatement of cerebral blood flow autoregulation that is often lost post-injury, [189,190] decreasing intracellular calcium accumulation, [191] decreasing brain edema, [188] decreasing free radical generation and associated lipid peroxidation, [192] improving mitochondrial function, [191] blocking excitotoxic effects of glutamate and other excitatory amino acid neurotransmitters, [193] diminishing inflammatory responses, [188,194] and preventing apoptosis. [188] Pharmacological interventions immediately post-injury, which result in decreased deaths of brain neurons, are expected to ultimately have the greatest impact on the long-term outcome of TBI patients. However, the findings of efficacy of tested interventions has been so limited to date, there are few choices for acute interventions at this point.

The clinicians managing the long-term consequences of TBI (e.g. physiatrists, neuropsychologists, neurologists, psychiatrists, occupational therapists, and physical therapists) are usually not involved in the care of the patient immediately following a traumatic event. For those managing the long-term consequences of TBI, the development of the field has been stunted to date because there has not been a comprehensive heuristic characterization of TBI that would organize our understanding of how to approach the pharmacologic management. A careful look at the literature would suggest that TBI patients have lesions that affect several domains of behavior, including psychiatric disturbances (psychosis/mood disturbances), cognition, and impulse control (including aggression). In fact, behavioral changes are potentially the most significant problem in the rehabilitation of individuals with TBI. [195] In a meta-analysis of the literature on psychiatric disturbances following TBI, the post-TBI incidence of: (1)

psychosis was 20%, (2) depression was 15-33%, (3) mania was 9%, (4) PTSD was 13-27%, and (5) aggression was 33-38%. [196] That particular review excluded studies that focused on cognitive disturbances. One can imagine that each of these domains is associated with interruption of specific neuronal pathways, and may require unique approaches to their pharmacologic management. In individual patients, it is likely that one or multiple brain circuits are affected. Further characterization of the specific circuits that are impaired may give guidance on how to approach pharmacologic management. However, at present we can only rely on the information available for pharmacological targeting of specific behavioral domains.

b. Pharmacological interventions to diminish the immediate extent of the injury/neuronal death

There are a growing number of pharmacological interventions available for administration immediately after traumatic brain injury being evaluated for efficacy. [11,197] One non-pharmacological intervention with some merit is hypothermia. Both animal studies and clinical trial suggest that moderate hypothermia may reduce disability resulting from TBI. [198]

The basic science necessary for establishment of acute pharmacological interventions is developing rapidly. Several pharmacological classes have been examined for their effects on recovery from traumatic brain injury based upon pre-clinical studies, including serotonin (5-HT)-1A receptor agonists, dopamine agonists, calcium channel blockers, NMDA antagonists, corticosteroids, bradykinin receptor antagonists, antidiuretic hormone agonists, cannabinoids, and free radical scavengers. [11] Despite basic science studies that suggest potential clinical benefits, a careful meta-analysis of these various pharmacological approaches demonstrates only marginal benefits. For example, if amantadine is administered within the first three days following traumatic injury, there appears to be a significant improvement in arousal. [199]

While results with NMDA antagonists have generally been disappointing, [200] results with traxoprodil (CP-101,606), a non-competitive NMDA receptor antagonist selective for the NR2B subunit of the NMDA receptor for which good brain penetration has been demonstrated, have been more promising. [201,202] The initial report assessed the safety, pharmacokinetics, and tolerability of CP-101,606 infused for various durations beginning 12 hours after brain injury in patients who had suffered either an acute moderate or mild TBI (Glasgow Coma Score, GCS; 9–14) or hemorrhagic stroke. A total of 53 subjects (45 with TBI and 8 with stroke) were randomized in a double-blind fashion to receive CP-101,606 or placebo (4 drug:1 placebo). [201] Drug or placebo was administered by intravenous infusion (0.75 mg/kg/hr) for 2 hours and then stopped (n = 25) or continued for 22 hours (n = 4) or 70 hours (n = 24) at a rate of 0.37 mg/kg/hr. Animal studies predicted the therapeutic concentration to be 200 ng/ml. This conclusion was achieved within two hours of initiating treatment and was sustained as long as drug was infused. All the patients tolerated their drug/placebo treatment, and there were no clinically significant cardiovascular, hematological, or neurobehavioral disturbances were observed. A second double-blind, placebo-controlled study was conducted with traxoprodil in subjects with computed tomography scan evidence of severe TBI (GCS 4–8) designed to evaluate the efficacy and safety of intravenous infusion of traxoprodil administered for 2 h at 0.75 mg/kg/h then continuing for 70 h at 0.37 mg/kg/h for a total of 72 h, in subjects diagnosed with a severe traumatic head injury with the primary endpoint assessment Glasgow Outcome Score (GOS) at 6 months. A total of 404 patients, aged 16–70, were treated within 8 h of injury (N=198 with traxoprodil and N=206 with placebo). At the 6-month endpoint there were no differences in the GOS between groups (44% vs. 36%, p=.07). Similarly, the mortality rate with traxoprodil treatment did not differ between groups (p=.08). Clearly, trends for efficacy were present, but further studies will need

to be performed to be certain that this intervention is useful.

Basic science suggests another promising approach, the use of statins (also known as 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors). [203,204] Statins are thought to have a variety of effects that may be beneficial interventions for TBI including: (1) increasing cerebral blood flow, (2) inhibition of neuroinflammation, (3) decreasing neuronal injury and apoptosis, (4) increasing neurogenesis and synaptic plasticity, and (5) angiogenesis. [205] In addition, in the controlled cortical impact rodent model of traumatic brain injury, rats treated subchronically (two weeks) with orally gavaged atorvastatin or simvastatin showed evidence of diminished loss of cells in the hippocampal CA3 region at day 35. [204]

Despite these promising findings in animal models, the only clinical trial using a statin, rosuvastatin, showed limited benefit. [206] In this double-blind randomized clinical trial patients between 16 and 50 years of age with TBI (GCS of 9–13 and an intracranial lesion demonstrated by computed tomography), 23 patients were randomized to receive either 20 mg rosuvastatin (N=8) or placebo (N=13) orally (nasogastric tube) immediately following acute stabilization and daily for 10 days. Routine treatment at admission included saline solution 0.9%, gastric protector (omeprazole 40 mg/day), analgesic (ketorolac 30 mg/12 h), and anticonvulsant for a period of 48 h (diphenylhydantoin, loading dose 15 mg/kg, maintenance 100 mg/8 h). Haloperidol or risperidone was used as antipsychotic drug in case of agitation. For intubation, diazepam (2-10 mg) plus rocuronium (0.6 mg/kg) was used. There was possibly some benefit measured for Galveston Orientation Amnesia Test (positive improvement in 2/8 with rosuvastatin and 1/13 with placebo). It appears there was a modest benefit on the Disability Rating Scale (DRS) at the time of discharge (mean score at release with rosuvastatin was 16 and 8 with placebo, p=.004). This effect was less obvious at the 3-month follow-up, and no longer

was statistically significant. The fact that the rosuvastatin was administered orally raises the question whether a high enough dosage was used to obtain sufficient brain levels to test the role of statins in recovery from TBI. Certainly, further clinical trials of statins are warranted.

One of the best studied and potentially most promising compounds for neuroprotection following TBI is progesterone. In a meta-analysis of animal studies of the neuroprotective effects of progesterone from 119 publications, 18 studies were identified that induced an experimental brain injury, administered progesterone, measured the lesion volume, and contained primary data. [207] In both cerebral ischemia and traumatic brain injury models, a significant benefit of progesterone was observed. Specifically, progesterone reduced lesion volume in a dose-dependent manner. The benefits of progesterone were limited to use in the first 2 hours following cerebral injury in these animal models, suggesting that benefits in humans would also be best if initiated very early in treatment.

With such a significant potential benefit demonstrated in animal studies, it is not surprising to see that clinical trials of progesterone also demonstrate promise. Two significant clinical trials have already been published. [208,209] In a large double-blind, placebo-controlled trial (using the acronym ProTECT) of the use of a progesterone infusion (initial loading dose of 0.71 mg/kg of progesterone for the first hour, then 0.5 mg/kg per hour for the remainder of 3 days) in individuals with GCS of 4-12 seen within 11 hours of acute brain trauma. [208] A total of 77 patients received progesterone infusions and 23 received placebo infusions. Thirty days after each patient's injury, blinded outcome examiners used the Extended Glasgow Outcome Score (EGOS) and the DRS to assess each survivor's functional status. Those with a GCS of 4-8 did not fare better with progesterone than placebo (27% had a EGOS score compatible with moderate or good recovery compared versus 21% of the progesterone group). However, those

with a baseline GCS of 9-12 demonstrated significant improvement in outcome measures with progesterone (56% randomized to progesterone and 0% randomized to placebo had moderate to good recovery, p=.02). Similar findings were present with the use of the DRS.

In a larger study performed in China, 159 patients (N=82 for progesterone and N=77 for placebo) evaluated within 8 hours of injury and with a GCS $\leq$8 were enrolled in a prospective, randomized, placebo-controlled trial of progesterone administered at 1.0 mg/kg by intramuscular injection each 12 hours for 5 consecutive days. [209] The primary endpoint was the GOS score 3 months after brain injury with secondary efficacy measures of the modified Functional Independence Measure (FIM) score and mortality. A 6-month follow-up also included the GOS and the modified FIM scores. At 3 months the GOS scores demonstrated benefit of use of progesterone compared with placebo. The modified FIM scores in the progesterone group were higher than those in the placebo group at both 3-month and 6-month follow- up ($p<.05$ and $p<.01$). The mortality rate of the progesterone group was significantly lower than that of the placebo group at 6-month follow-up ($p<.05$). Adverse events associated with the administration of progesterone were not observed.

These two studies used significantly different doses of progesterone: (1) 0.5 mg/kg/hour intravenously and (2) 1 mg/kg/12hr intramuscularly. In the first study the effective dose used is 6 mg/kg/12 hour, equivalently at least six times that of the second study. In the second study the results were potentially even more dramatic. This raises the question about what the appropriate dose is for optimal response. Also, the second study focused on treatment of more severely impaired individuals. These results suggest that future studies are justified, and argue for acute administration of progesterone immediately following a TBI.

Another compound, which has been touted as a potential neuroprotective and therapeutic

agent over the last two decades, is cytidine-5'-diphosphate-choline (CDP-choline). Basic studies using rats in the lateral controlled cortical impact model demonstrate that CDP-choline (100mg/kg), administered daily for 18 days beginning 1 day post-injury, diminished the cognitive (Morris water maze performance) deficits. [210] CDP-choline also decreased the TBI-induced increased sensitivity to the memory-disrupting effects of scopolamine. Microdialysis studies demonstrated that CDP-choline administration resulted in increased extracellular levels of ACh in dorsal hippocampus and neocortex in normal, awake, freely moving rats. In addition, a meta-analysis of the use of CDP-choline concluded that treatment with oral CDP-choline within the first 24 hours after onset in patients with moderate to severe stroke increases the probability of complete recovery at 3 months. [211]

Clinical studies on the use of CDP-choline for treatment of TBI raise the possibility of potential benefit. An early report of use of CDP-choline suggested it could improve recall and reduce post-concussional symptoms following mild TBI. [212] A subsequent report on two cases where CDP-choline was given to individuals with head injuries following horse-riding accidents also suggested some benefit. [213]

In an open-label trial, CDP-choline was administered (intravenously in divided doses until oral doses were tolerated) at a rate of 4 gm in the first 2 days, then 3 gm for the second 2 days, then 2 gm daily until discharged. [214] After discharge from the hospital, patients receive CDP-choline at 200 mg every 8 hours orally. The percentage of patients with a good recovery as defined by the 3-month GOS Score was higher in the CDP-choline group (77% vs. 51% for placebo controls). Very promising results were also seen when 7 patients with a severe TBI (GCS<8) and severe memory problems were given CDP-choline one hour before non-invasive ^{133}Xenon inhalation was given to measure cerebral blood flow. [215] All patients showed

significant hypoperfusion in the inferoposterior temporal lobe of the brain at a resting state, which disappeared after administering CDP-choline. Also, 10 patients were enrolled in a double-blind, placebo-controlled second phase of the study which included 3 months of treatment with neurocognitive rehabilitation and either CDP-choline (1 gm daily) or placebo. CDP-choline administration resulted in improvements in both verbal fluency and Luria's Memory Words-Revised ($p < .05$).

A major test of the effectiveness of CDP-choline in TBI is in progress. [216] The Citicoline Brain Injury Treatment (COBRIT) trial is a randomized, double-blind, placebo-controlled, multi-center trial of the effects of 90 days of citicoline (CDP-choline) on functional outcome in patients with complicated mild, moderate, and severe TBI. In all, 1292 patients will be recruited over an estimated 32 months from eight clinical sites with random assignment to citicoline (1000 mg twice a day) or placebo (twice a day), administered enterally or orally. The 90-day primary outcome measures include a core test battery of: the California Verbal Learning Test II; the Controlled Oral Word Association Test; Digit Span; EGOS; the Processing Speed Index; Stroop Test (parts 1 and 2); and Trail Making Test (parts A and B). Secondary outcomes include survival, toxicity, and rate of recovery. Recruitment was expected to be completed in 2010, but results have not been published to date.

There is considerable evidence from animal studies accumulating that erythropoietin (EPO) is neuroprotective after different types of cerebral tissue injuries such as ischemia, subarachnoid hemorrhage, or traumatic brain injury. [217] These promising results have led to the initiation of clinical trials, some of which are in progress currently. In the first published trial, a randomized, double-blind, placebo-controlled single-center trial was performed in adults with an admission GCS < 13 and evidence of TBI by computerized tomography imaging. [218] Patients received

either EPO (40,000 Units IV) or placebo administered within 6 hours of the time of injury. Baseline and daily serum S-100B and Neuron Specific Enolase (NSE) levels, markers of the severity of brain injury, were measured over the first 5 days. EPO did not impact NSE (p=.89) or S100 B (p=.53) levels compared to placebo. In this pilot study, only a single EPO injection was given, and long-term follow-up measures were not obtained. Clearly, these findings do not preclude the possibility of benefits being identified in future studies.

C. Pharmacological management of stable traumatic injuries

a. Pharmacotherapy of Cognitive Dysfunction in TBI

Mild traumatic brain injuries are most likely to exhibit long-term effects on memory, complex attention/working memory and executive function, as well as the speed of processing. [187,219,220] Recent reviews characterize the use of psychotropic medications in patients with stable traumatic brain injuries. [221,222] Methylphenidate and amantadine have been identified as dopamine agonists with positive effects on multiple cognitive domains including attention, memory, executive function, sensory-perceptual-motor skills, and global cognition. The most robust findings are associated with the use of methylphenidate. Although the studies consistently report improvement with methylphenidate, the benefit on attention may not be as robust as found in the treatment of attention deficit hyperactivity disorder. [223] Drugs that release dopamine improve attention and working memory by the stimulation of D1 dopamine receptors in the dorsolateral prefrontal cortex. [224] In primates there is an inverse-U-shaped curve that defines the relationship between the available dopamine and working memory. As a result, drugs that cause release of dopamine (e.g. methylphenidate, d-amphetamine or amantadine) would be expected to have a similar dose-response relationship. Certainly, the possibility of such a pharmacological relationship should be entertained when evaluating response to this class of medications. In

addition to the benefits of indirect acting dopamine agonists such as methylphenidate and amantadine, there is at least some evidence that the direct dopamine agonist bromocriptine may improve executive function, processing speed and attention in patients with traumatic brain injuries. [225] A dose-response relationship for this effect has not been characterized.

Acetylcholinesterase inhibitors (AChEIs) are known to improve cognitive function of patients with Alzheimer's disease, a condition associated with very striking loss of cognitive function. Based upon this role they have been proposed as treatments for cognitive dysfunction in TBI. [226] However, the treatment of TBI with a cholinesterase inhibitor is not identical to treatment of Alzheimer's disease because in TBI there is not progressive loss of neurons associated with this specific neurotransmitter system. Despite this basic difference, there is a possibility that cognitive deficits resulting from trauma may respond to AChEIs. The most commonly prescribed AChEI, donepezil, has been shown to improve cognitive recovery of individuals with stable traumatic brain injuries. [226] Specifically, both verbal learning and attention responded to donepezil over a three-month period. In a retrospective review of the treatment response of over 100 patients with stable traumatic brain injuries, donepezil, galantamine, and rivastigmine had equal efficacy in improving function. [227] Unfortunately, this study did not prospectively evaluate changes in cognition. The improvements were thought to be secondary to better vigilance and attention. While oral physostigmine was ineffective in improving memory or attention in TBI patients, it is not clear if oral physostigmine would result in sufficient acetylcholinesterase inhibition to be expected to produce benefits and direct measurement of cholinesterase inhibition did not occur. [228,229]

Animal studies demonstrate that at least in the hippocampus, stress and depression decreases and antidepressant therapy increases brain derived neurotrophic factor levels and thereby

increases sprouting of dendrites. [230,231] Based upon this information, the possibility that antidepressants could be a mechanism to improve recovery from a TBI has been raised. [232] While no potential mechanism for promoting recovery from a TBI should be overlooked, antidepressant are very commonly given to individuals in the recovery period and no obvious cognitive benefit has yet been described. Also, interpretation of the results of studies evaluating the effects of antidepressants on cognition in TBI would be complicated by the need to correct for improvements in mood. While the use of antidepressants to improve cognition has not been fully evaluated; if benefit is present, it obviously is not of great magnitude.

A novel approach to the enhancement of cognitive performance is the use of the alpha 2-adrenergic agonist guanfacine. [233] In a test of the hypothesis that administration of an alpha-2 adrenergic agonist might improve working memory after mild TBI, 13 individuals 1 month after injury producing a mild TBI and 14 healthy controls were challenged with guanfacine (2 mg) and placebo prior to administration of an N-back task. Guanfacine improved working memory performance in the mild TBI group (2-back; p=.02), but not in the control group. The improved working memory function was accompanied by activation of the prefrontal cortex.

Antiepileptic mood stabilizers may produce mild cognitive impairment and appear only to improve cognition by diminishing the frequency of seizures. [234,235] The cognitive effects of valproic acid are subtle enough that they are not detectable by a battery of neuropsychological tests (assessing motor functioning, memory, attention/concentration, and general intelligence) in the first six months post injury.

In summary, it does appear that mild benefits can be identified for the use of either stimulants or AChEIs for improving cognitive function in individuals with TBI. However, there is no current evidence that these benefits will result in reversal of the underlying deficits.

b. Pharmacotherapy of Mood Disturbance in TBI

Depression is a very significant problem following TBI, occurring in up to one-third. [196] In a retrospective review of 867 patients requiring hospitalization on an acute rehabilitation unit, patients that required antidepressant medication treatment for depression while inpatients immediately following a head injury had their hospitalization length of stay prolonged by an average of 6 days in comparison to those that did not receive antidepressant treatment or receive a diagnosis of depression (p=.04). [236] In fact, as summarized by Ashman, et al. [237] post-TBI depression has been associated with greater functional disability, reduced participation in activities of daily living, less social and recreational activity, less employment potential, increased caregiver burden, greater sexual dysfunction, lower ratings of health, poor subjective well-being, poorer QOL, and increased rates of suicidal ideation. Despite that knowledge, there have been relatively few studies of antidepressant therapy in TBI. One of the larger open-label trials specifically used operationally defined criteria: (1) response is a 50% reduction in Hamilton Depression score, and (2) remission was defined by a Hamilton Depression score of $\leq$7. [238] Subjects with major depression following mild (GCS of 13-15) -to moderate (GCS <13) TBI were treated with open-label citalopram. The first 29 subjects recruited underwent a six-week trial of fixed dose citalopram 20 mg/day. Due to a low rate of response, the trial period was then extended to 10 weeks with a flexible dosing schedule, starting at 20mg/day, and titrating to a maximum of 50 mg/day (N= 54). The mean HAMD at baseline and 6 weeks was 24 and 16, respectively (t=7.16, p<.0001). The mean HAMD at 10 weeks was 13 (t=7.32, p<.0001). At 6 weeks, 54 subjects were assessed with 28% demonstrating response and 24% meeting criteria for remission. At 10 weeks, 26 subjects were assessed with 46% meeting criteria for response and 27% identified as in remission.

Similar results were found in a small 8-week, nonrandomized, single-blind, placebo run-in trial of sertraline conducted in 15 patients diagnosed with major depression between 3 and 24 months after a mild traumatic brain injury. [239] By the end of the treatment period, 13 (87%) had a decrease in the HAM-D score of >50% ("response"), and 10 (67%) achieved a score of $\leq$7 ("remission").

A larger 10-week double-blind randomized placebo-controlled trial of sertraline (daily oral sertraline in doses starting at 25mg and increasing to therapeutic levels up to 200mg) did not demonstrate benefits for sertraline. [237] However, the proportion of the patients with moderate or severe TBI was greater in the placebo group. It is already known that cognitive deficits diminish the likelihood of antidepressant response. [164,165] In fact, in a study of depression treatment with amitriptyline (beginning at 100mg daily and increasing to a maximum of 250 mg daily), 13 mild TBI patients matched for age, sex, duration of symptoms and HAM-D scores with an equal number of individuals who were functionally depressed, were less likely to demonstrate response (4 of 13 of the TBI group had a 50% drop in HAM-D baseline scores, but 11 of 13 controls; X^2=5.67, df=1, p<.01). [240] Amitriptyline doses for the 2 groups were equivalent (TBI group was 158 mg and control group was 179 mg).

It is generally assumed that once remission is achieved the antidepressant dose required to induce remission will continue to be effective. However, in the only study to directly address maintenance treatment in TBI patients, continuation therapy was no more effective than placebo. [241] Following an open-label trial of citalopram (20 mg to 50 mg daily) in patients with mild to moderate TBI, 25 subjects (39%) met criteria for remission (HAM-D $\leq$7). Of those, 21 were randomly assigned to either same-dose citalopram (at the same dose that resulted in remission; N=10) or placebo (N=11) and followed monthly over 40 weeks. The groups did not differ in

relapse rates (defined as HAM-D score ≥ 16; citalopram: 50% vs. placebo: 55%; Fisher exact test, p=.84) or time to relapse (log rank test $\chi 2$=.15, p=.70). It may be premature to rely on these findings because this is such a small study. Clearly, further studies should be initiated.

Individuals with TBI or other brain lesions sometimes exhibit pathological crying (involuntary and uncontrollable outbursts of crying typically triggered by emotionally relevant situations). [242] Treatment of this condition with either citalopram (10-40 mg daily; N=13) or paroxetine (10-40 mg daily; N=13) in an open-label trial resulted in rapid (within 1±3 days) and dramatic improvement of the severity of pathological crying or laughing as assessed with clinical interviews associated with symptom provocation (p<.001). The very rapid response suggests that the pathophysiology may differ from Major Depressive Disorder.

In addition to depression, up to 9% of TBI patients exhibit episodes of mania. [196] While case reports are available describing the use of antipsychotics or various mood stabilizers for treatment of mania secondary to TBI, there are no controlled trials to evaluate this pharmacotherapy. As a consequence, it seems prudent based upon the added benefit of decreased seizure risk to focus treatment on anticonvulsant mood stabilizers, but recognize that most or all known treatments for mania are likely to benefit some patients.

c. Pharmacotherapy of Aggressive Behavior/Poor Impulse Control following TBI

The most important and difficult to treat consequence of TBI is aggressive behavior, which is present in approximately one-third of TBI patients. [196] The pharmacological management of this behavior has been addressed with multiple classes of psychotropics including: anticonvulsants, antidepressants, antipsychotics, benzodiazepines, beta-adrenergic blockers, buspirone (partial 5-HT-1A agonist), and lithium. [243] Fleminger, et al. [243] reviewed the available literature on the management of aggression following TBI, and concluded that there is insufficient evidence at

present to recommend any treatment for TBI-associated aggression. One of the main reasons for the inability to provide recommendations is the lack of large controlled trials that would allow confident conclusions. Other reviews of the management of aggression following TBI arrive at similar conclusions. [10,244] Despite the lack of clarity of the literature, there is some evidence for benefit with the use of high doses of beta-adrenergic blockers, SSRIs, valproic acid, buspirone. For example, in a randomized, placebo-controlled trial of propranolol (up to 420 mg/day) in 21 individuals with severe TBI and agitation, patients experienced a significant reduction in intensity of the most severe episode per week ($p<.05$), but no significant change in frequency of episodes. [245] Similar findings were identified for the use of another beta-adrenergic agent, pindolol (60– 100 mg/day), in a double-blind, placebo-controlled crossover study of violent behavior in a mixed population of which 5 of 11 patients had TBI. Although, in this study the number and severity of assaultive episodes decreased ($p<.05$). [246]

SSRIs are known to have some ability to control agitation/hostility and aggression. [247] In fact, in a study of 159 participants (ages 30 –50 years, 50% female) who scored high on 2 measures of hostility (measured by subscales of the Buss–Durkee Motor Aggression Scale and the Cook–Medley Hostility Scale) and with no current major Axis I diagnosis were randomly assigned to 2 months of citalopram (40 mg, fixed–flexible dose) or placebo. Treated participants showed larger reductions in state anger ($p<.01$), and hostile affect ($p<.02$). [247] Consistent with this finding, 3 patients with TBI and aggression responded to open-label trials of either sertraline (100-150 mg) or paroxetine (20 mg) over 2-4 weeks. [248] Also, in an 8-week single-blind trial of the use of sertraline (25-150 mg) in 16 patients with mild TBI and depression, scores on the Brief Anger and Aggression Questionnaire dropped significantly (from 9.3 at baseline to 6.5 post-treatment; $t=2.33$, $df=14$, $p<.05$), as did the HAM-D scores. Scores of irritability and loss of

temper on the Head Injury Symptom Checklist also improved during treatment in 9 of the 16 participants. Also, in 8-week open-label trial of sertraline in 13 patients who experienced problems with irritability and aggression following TBI demonstrated significant reduction in irritability and aggressive outbursts in 9 of the 13 patients on the Overt Aggression Scale-Modified for outpatients ($t=3.75$, $df=9$, $p<.01$). [249]

Anticonvulsants and other mood stabilizers are known to diminish aggressive behavior. [250,251,252] Efficacy for phenytoin, carbamazepine and valproic acid appears to be equivalent for management of impulsive aggression. [252] However, there have been limited studies of the efficacy of anticonvulsants for management of aggression in patients with TBI. In fact, the published data is based upon small case series or case reports. [253,254,255,256] The case reports demonstrate that valproic acid may have utility in management of severe aggressive behavior at doses consistent with management of mania. The largest study of the use of valproic acid included 11 patients, 9 had TBI and 2 were post-stroke. [256] In this case series, valproic acid treatment (average daily dose of 1818 mg; mean serum valproic acid level of 86 ug/ml) resulted in a mean CGI improvement score of 1.9. Three patients were rated as extremely improved, 7 patients were much improved, and 1 patient was minimally improved. There appeared to be a relationship between the serum valproic acid level and the improvement scores on the CGI ($r=-0.73$, $p<.01$), that is the higher the serum level the greater the improvement. Further studies are warranted.

Another anticonvulsant, carbamazepine, is sometimes used for management of agitation/aggression in TBI. [10,244,257] In the largest study to date of the use of carbamazepine in the management of patients with TBI, 10 patients with agitation and anger outbursts following a severe TBI, were treated in a prospective open trial with carbamazepine (400 to 800 mg per day)

for 8 weeks. Group analysis demonstrated a statistically significant improvement of a score made up from six target items from the Neurobehavioral Rating Scale-Revised (NRS-R; hyperactivity-agitation, mood liability, irritability, disinhibit ion, excitation, and hostility). Blood levels at the end of the treatment period were relatively low for behavioral control (5.6 ug/ml). Improvement was seen in both the NRS-R and the Agitated Behaviour Scale ($z=-2.3$, $p<.02$; $z=-2.2$, $p<.02$, respectively), mainly for the symptoms of irritability and disinhibition. Global cognitive functioning, as measured by the Mini Mental Status Examination was not affected.

Similar data is available for the use of lithium in management of aggression secondary to TBI. [258,259,260] Case reports suggest benefit of the use of lithium, which is corroborated with a case series. [260] Lithium carbonate was tried in 10 cases of severe, unremitting, aggressive, combative or self-destructive behavior. A positive response was seen in 7 of the 10, although in one case the patient regressed after initial stabilization. The response was described as dramatic in 5 cases. In this case series, standard outcome assessments were not used and therefore the only indication of positive response was the observation of the clinicians.

Buspirone, a partial 5-HT-1A agonist, has been reported to have efficacy in modulating aggression in a variety of settings. [261] Case reports indicate benefits with the use of buspirone in doses up to 60 mg daily. [262,263] A retrospective review of 10 cases at the Austin State Hospital for which a 3-month observation period was possible, demonstrated that 9 of 10 had significant improvement with 6 showing a 50% reduction in symptoms. [261] Interestingly, 6 of 10 had a temporary worsening of symptoms before improvement. A prospective open-label trial in 13 patients with mild to moderate TBI using buspirone at doses from 10-35 mg daily also found benefit as measured on the NRS, although in only 7 of the 13 patients. [264] The 6 that did not have

improvement included 5 that could not tolerate buspirone because of headaches (N=2), light-headedness (N=2) or a rash (N=1). Large scale studies that would be definitive are absent.

The use of antipsychotics for management of agitation and aggression in non-psychotic patients has garnered increasing criticism. However, antipsychotics are helpful for control of aggressive behavior in some individuals. Large scale, controlled trials have not been performed, but case series and open-label studies suggest potential benefits. For example, quetiapine in doses from 25 to 300 mg (X=111 mg daily) was tested in 7 patients that were at least 3 months post-injury. [265] Primary efficacy measures included the Overt Aggression Scale Modified for Outpatients and the CGI. Secondary measures were the Neurobehavioral Functioning Inventory, measures of extrapyramidal function (Simpson-Angus Scale, Barnes Akathisia Rating Scale and Abnormal Involuntary Movements Scale), and the Repeatable Battery for the Assessment of Neuropsychological Status. Quetiapine resulted in an 85% reduction in the Overt Aggression Scale score (p=.002), and neuropsychological measures actually improved by 8% (p=.03). Second generation antipsychotics are preferable to first generation antipsychotics in this setting because individuals with TBI may be more vulnerable to the cognitive side effects of first generation antipsychotics and the risk of the development of tardive dyskinesia. [12,266,267] Low potency antipsychotics such as thioridazine and chlorpromazine are known to exhibit significant anticholinergic activity, and therefore would be most likely to adversely affect cognition. However, there is limited data directly addressing the cognitive effects of antipsychotics in TBI. What is known is consistent with studies in patients with schizophrenia where a significant literature documents the modest cognitive benefits of second-generation antipsychotics over first generation compounds. [268,269] A possible exception to this rule is clozapine. [270] The limitations of

clozapine on cognition and its propensity to decrease the seizure threshold suggest that it should not be used in a TBI population.

d. Pharmacotherapy of Psychosis in TBI

Psychosis secondary to TBI occurs in approximately 20% of patients. [196] Treatment of this condition should follow the same paradigm for management of psychosis in other conditions. [271] Concerns about the use of antipsychotics in patients with TBI are discussed in the section on treatment of aggression. Based upon the issues of minimizing extrapyramidal syndromes and potential cognitive dysfunction, it is best to use second generation antipsychotics. It has also been recommended that starting with low doses and raising the dose slowly are useful guidelines. However, these recommendations cannot be definitive, because large scale, controlled trials of antipsychotics in psychotic TBI patients are lacking.

D. Guidelines for Clinical Care

Our current understanding of the pharmacological management of PTSD is that pharmacotherapy should begin with an antidepressant trial. Most antidepressants have demonstrated efficacy for management of PTSD; and, to date, the evidence suggests that each is equally effective for each of the PTSD symptom clusters. There does appear to be a difference in responsivity based upon the duration of PTSD symptoms, and as a consequence Vietnam era veterans have generally been less responsive to a wide variety of treatments offered in the past two decades. However, there is no definitive evidence that the type of traumatic event responsible for the PTSD determines whether response to pharmacological treatment will occur. The literature suggests that some interventions (e.g. ketamine, morphine and propranolol) are likely to be effective only immediately following a traumatic injury, i.e. as secondary prevention.

There is no evidence, however, that once Acute Stress Disorder is established the pharmacological treatment should differ from treatment of chronic PTSD.

Based upon safety and reasonable expectation of efficacy, an SSRI should be the best first step. The choice of which SSRI to use would not be based upon known differences in effectiveness. Tolerability among SSRIs does not substantially differ among the various agents. It is best, then, to begin an SSRI with which the clinician is familiar. The individual SSRI should be started at a low dose and systemically increased at approximately monthly intervals until a maximum tolerated dose is obtained or the patient exhibits significant response. Dosage changes should be based upon objective criteria, such as a PTSD Symptom Checklist, when possible. If significant improvement is not observed within the pre-determined intervals, the dosage should be increased further. While maximum dosages should generally be within the FDA-approved guidelines, there may be some patients that require higher dosages. If the maximum dosage of a particular SSRI is obtained with less than a significant response, the possibility of switching to another antidepressant or using an augmenting agent should be considered. The choice of augmenting agent to be used is not well established at this time. However, the best evidence supports the use of the alpha-1 adrenergic antagonist prazosin. If addition of prazosin is not of benefit, then use of a second-generation antipsychotic (i.e. risperidone, olanzapine, or quetiapine) should be offered. While it is likely that all second generation antipsychotics would be beneficial, sufficient data are lacking for other drugs in this class (i.e. aripiprazole, asenapine, iloperidone, paliperidone, and ziprasidone). Other augmenting agents (e.g. buspirone, mirtazapine or trazodone) should be considered. In general, the guidelines for augmenting the treatment of PTSD should resemble that of the treatment of depression with the exception of the use of prazosin. The duration of treatment required for

resolution of chronic PTSD is not known, but there is clear evidence that removal of maintenance pharmacotherapy is likely to result in symptomatic relapse. It would be prudent to continue treatment of PTSD for at least a year after the patient is able to resume a full return to usual functioning.

The pharmacologic management of TBI is less well understood and characterized, although there is rapid development of the heuristic models that should result in appropriate pharmacotherapy. At present there is no consensus on what interventions to use in the initial stages of recovery from a traumatic event, but hypothermia and administration of progesterone or CDP-Choline have produced the most promise to date. In time, this will likely become the most important intervention because of the possibility of preventing tissue loss. Once the effects of the injury are chronically established, our current understanding the best approach to the pharmacologic management of TBI is to target the primary behavioral dysfunction. If short-term memory impairment is the primary finding a trial with an AChEI is most appropriate. Attentional or working memory impairments are best approached with the use of stimulants. If psychotic symptoms (e.g. hallucinations or delusions) are prominent, antipsychotic agents should be prominent in the therapeutic regimen. If depression is prominent, an antidepressant is warranted. If a manic syndrome is present, a mood stabilizer or antipsychotic would likely be helpful. Impulsivity and aggression are likely to respond to a variety of interventions. For example, SSRI antidepressants are known to decrease aggression and impulsivity in animal models, and are often helpful clinically. Lithium and mood-stabilizing anticonvulsants have anti-aggressive properties that may be useful in specific individuals. Some individuals may respond to beta-blockers in high doses. Other individuals may require the use of antipsychotics, if the other compounds are ineffective.

C. Suggestions for future work

Characterization of the pharmacotherapy of PTSD is much better developed than that for TBI. However, the development of an effective, empirically derived algorithm for the treatment of PTSD is still ahead and likely will take many years. One of the most important reasons why the data for a robust algorithm is missing is the lack of availability, until now, of large populations of individuals with recent onset PTSD to develop such a paradigm. With the large numbers of individuals that have developed PTSD from the recent military conflicts, this period offers a unique opportunity to define the best treatment options. Further development of an algorithm will require direct comparisons of individual members of a pharmacological class, as well as head-to-head comparisons of different classes of agents. In addition, the potential for synergistic or at least additive effects of the combination of psychotherapeutic approaches with established pharmacotherapies should be investigated.

The treatment of the behavioral and psychiatric sequelae of TBI appears to require specifically addressing prominent symptoms complexes: cognitive deficits, mood disturbances, psychosis, and aggression. The specific complexes appear to respond to the established treatment modalities for these behavioral syndromes. The unique approaches to management of TBI are those that show promise to minimize the extent and severity of the neuronal loss post-injury. Further characterization of the various classes of compounds that have appear to have neuroprotective effects will be the focus of future work in the management of TBI.

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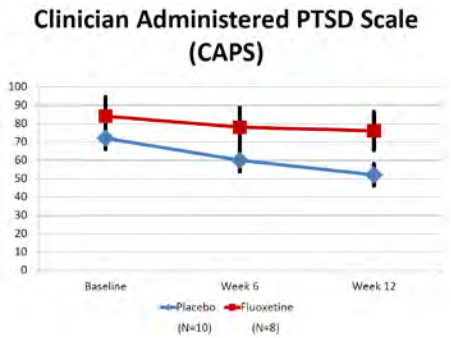
Abbreviations List

CAPS	Clinician Administered PTSD Scale
CAPS-2	Clinician Administered PTSD Scale, Part 2
CDP-Choline	Cytidine-5'-diphosphate-choline
CGI	Clinical Global Impression
CR	Controlled Release
DCS	D-Cycloserine
DoD	Department of Defense
DRS	Disability Rating Scale
EGOS	Extended Glasgow Outcome Score
EPO	Erythropoietin
FIM	Functional Independence Measure
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Score
IES	Impact of Event Scale
NE	Norepinephrine
NMDA	N-Methyl-D-Aspartate
NPY	Neuropeptide Y
NSE	Neuron Specific Enolase
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
PCL	PTSD Symptom Checklist
PTI	Peritraumatic Tonic Immobility

PTSD	Posttraumatic Stress Disorder
SCID	Structured Clinical Interview for Diagnosis
SPRINT	Short PTSD Rating Interview
SSRI	Selective Serotonin Reuptake Inhibitor
TBI	Traumatic Brain Injury
TOP-8	Treatment Outcome PTSD-8
VA	Department of Veterans Affairs

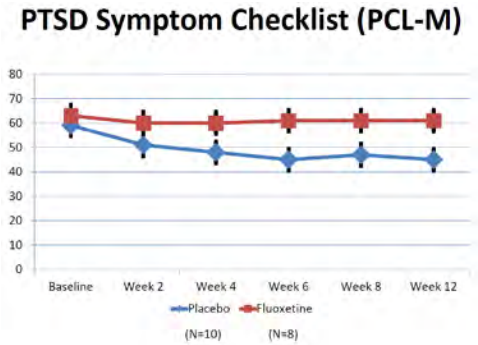
SUPPORTING DATA:

Fig. 1.



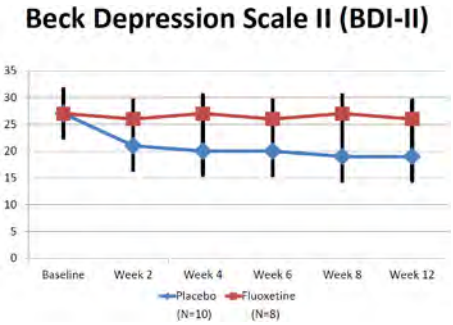
The primary outcome measure was the CAPS. Means are plotted with the last observation carried forward. However, significant dropout (6 from fluoxetine group and 4 from the placebo group) occurred in both treatment groups. Meaningful statistical analysis is not possible with those observations.

Fig. 2.



A secondary outcome measure was the PCL-M. Means are plotted with the last observation carried forward. However, significant dropout (6 from fluoxetine group and 4 from the placebo group) occurred in both treatment groups. Meaningful statistical analysis is not possible with those observations.

Fig. 3.



Another secondary outcome measure was the B. Means are plotted with the last observation carried forward. However, significant dropout (6 from fluoxetine group and 4 from the placebo group) occurred in both treatment groups. Meaningful statistical analysis is not possible with those observations.